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AHA PRESIDENTIAL ADVISORY

Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association

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ABSTRACT: Cardiovascular-kidney-metabolic health reflects the interplay among metabolic risk factors, chronic kidney disease, and the cardiovascular system and has profound impacts on morbidity and mortality. There are multisystem consequences of poor cardiovascular-kidney-metabolic health, with the most significant clinical impact being the high associated incidence of cardiovascular disease events and cardiovascular mortality. There is a high prevalence of poor cardiovascular-kidney-metabolic health in the population, with a disproportionate burden seen among those with adverse social determinants of health. However, there is also a growing number of therapeutic options that favorably affect metabolic risk factors, kidney function, or both that also have cardioprotective effects. To improve cardiovascular-kidney-metabolic health and related outcomes in the population, there is a critical need for (1) more clarity on the definition of cardiovascular-kidney-metabolic syndrome; (2) an approach to cardiovascular-kidney-metabolic staging that promotes prevention across the life course; (3) prediction algorithms that include the exposures and outcomes most relevant to cardiovascular-kidney-metabolic health; and (4) strategies for the prevention and management of cardiovascular disease in relation to cardiovascular-kidney-metabolic health that reflect harmonization across major subspecialty guidelines and emerging scientific evidence. It is also critical to incorporate considerations of social determinants of health into care models for cardiovascular-kidney-metabolic syndrome and to reduce care fragmentation by facilitating approaches for patient-centered interdisciplinary care. This presidential advisory provides guidance on the definition, staging, prediction paradigms, and holistic approaches to care for patients with cardiovascular-kidney-metabolic syndrome and details a multicomponent vision for effectively and equitably enhancing cardiovascular-kidney-metabolic health in the population.

Key Words: AHA Scientific Statements ■ chronic kidney disease ■ diabetes ■ metabolic syndrome ■ obesity ■ risk prediction ■ social determinants of health

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Summary

There is a high burden of poor cardiovascular-kidney-metabolic health in the population, which affects nearly all organ systems and has a particularly powerful impact on the incidence of cardiovascular disease. More guidance is needed on definitions, staging, prediction strategies, and algorithms for the prevention and treatment of cardiovascular-kidney-metabolic syndrome to optimize cardiovascular-kidney-metabolic health across diverse clinical and community settings.

TOP 10 HIGHLIGHTS OF THE CARDIOVASCULAR-KIDNEY-METABOLIC HEALTH PRESIDENTIAL ADVISORY

1. Cardiovascular-kidney-metabolic (CKM) syndrome is defined as a health disorder attributable to connections among obesity, diabetes, chronic kidney disease (CKD), and cardiovascular disease (CVD), including heart failure, atrial fibrillation, coronary heart disease, stroke, and peripheral artery disease. CKM syndrome includes those at risk for CVD and those with existing CVD.

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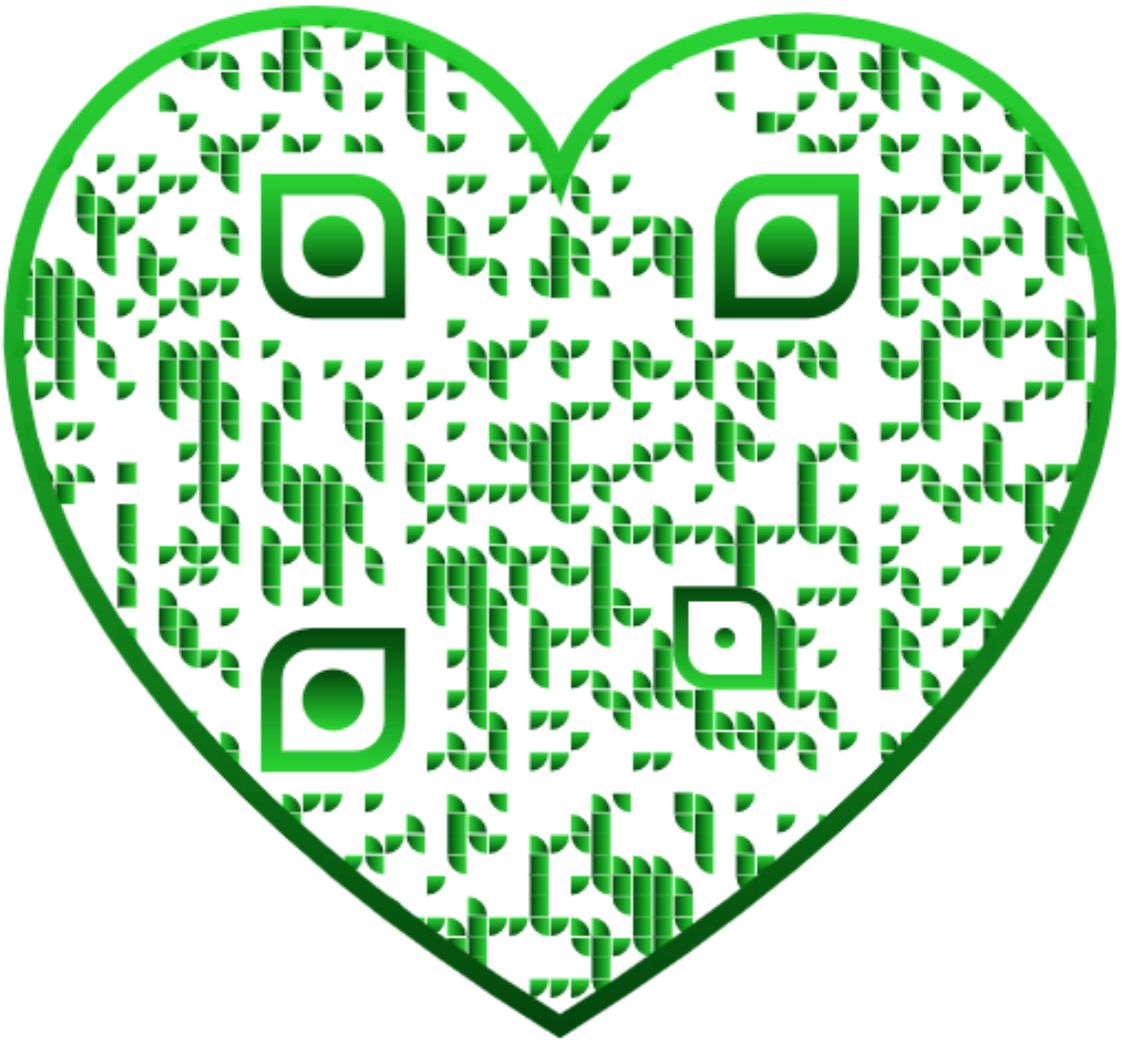

2. This advisory provides a CKM staging construct that reflects the pathophysiology, spectrum of risk, and opportunities for prevention and care optimization within CKM syndrome: stage 0, no CKM risk factors; stage 1, excess or dysfunctional adiposity; stage 2, metabolic risk factors (hypertriglyceridemia, hypertension, diabetes, metabolic syndrome) or moderate- to high-risk chronic kidney disease; stage 3, subclinical CVD in CKM syndrome or risk equivalents (high predicted CVD risk or very high-risk CKD); and stage 4, clinical CVD in CKM syndrome. In addition, risk-enhancing factors influence the likelihood of progression along CKM stages.
3. Screening for CKM risk factors is suggested across the life course to enhance approaches to prevention and management in both youth and adults, with the frequency and intensity of suggested screening linked to the CKM stage.
4. New approaches are described for predicting outcomes related to CKM syndrome, including assessing risk for both atherosclerotic CVD and heart failure and incorporating risk assessment starting at 30 years of age, which is reflected in a new CKM risk calculator.
5. Value- and volume-based strategies can reduce care fragmentation and improve interdisciplinary care for patients with multiple comorbid conditions within CKM syndrome and are outlined in this document.
6. Given the excess burden of CKM syndrome among individuals with adverse social determinants of health (SDOH) and the impact of SDOH on CKM syndrome management and outcomes, systematic SDOH screening is emphasized, as well as incorporating SDOH into risk prediction and addressing SDOH as part of clinical care model for patients with CKM syndrome.
7. Excess or dysfunctional adiposity should be addressed through lifestyle modification and weight loss to prevent progression and to facilitate regression along CKM stages.
8. A framework for optimizing CVD risk reduction and selecting cardioprotective antihyperglycemic agents (eg, sodium-glucose transport protein 2 inhibitors, glucagon-like peptide 1 receptor agonists receptor agonists) among patients with diabetes is provided, with sodium-glucose transport protein 2 inhibitors prioritized for those with CKD, existing heart failure, or high heart failure risk, and glucagon-like peptide 1 receptor agonist prioritized for those with uncontrolled hyperglycemia (hemoglobin A1c ≥9%), high insulin doses, or severe obesity (body mass index ≥35 kg/m^2). Combined use of sodium-glucose transport protein 2 inhibitors and glucagon-like peptide 1 receptor agonists should be considered for those with multiple CKM risk factors in the setting of CVD or high predicted CVD risk.
9. Clinicians are encouraged to measure urine albumin-creatinine ratio in addition to estimated glomerular filtration rate in those with CKD, diabetes, hypertension, and metabolic syndrome for fully characterizing CKD and CVD risk (particularly heart failure). Guidance is also provided for the appropriate use of kidney-protective therapies with resultant cardiovascular benefit (eg, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, sodium-glucose transport protein 2 inhibitors, finerenone).
10. A framework is provided for optimizing CKM health in the population, including enhancing education on CKM health; investing in research related to CKM syndrome; systematically assessing and addressing SDOH; improving obesity care and the availability of integrated teams to support lifestyle change and weight management; increasing equitable access to pharmacotherapies; supporting value- and volume-based interdisciplinary care models; applying proven implementation strategies within and across health centers; and developing partnerships to support the achievement of ideal cardiovascular health across diverse communities.

Cardiovascular-kidney-metabolic (CKM) health is the clinical presentation of the pathophysiological interactions among metabolic risk factors such as obesity and diabetes, chronic kidney disease (CKD) and the cardiovascular system.[1] The clinical implications of poor CKM health are significant, with potential for premature mortality, excess morbidity, multiorgan disease, and high health care expenditures driven largely by the burden of cardiovascular disease (CVD). The high prevalence of poor CKM health in the population is a public health emergency, but it is accompanied by a period of great opportunity. In addition to a growing understanding of the scientific underpinnings of CKM health, there is an expanding array of impactful therapies with beneficial metabolic and kidney effects, which also confer significant protection against adverse CVD events and mortality. However, to substantively improve CKM health and related outcomes, further guidance is needed regarding (1) a clear definition of CKM syndrome, (2) a CKM staging approach that can help reduce the likelihood of syndromic progression, (3) a risk prediction approach that reflects exposures and outcomes most relevant to CKM health, and (4) the optimal strategies for prevention and management of CKM-related adverse outcomes.

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There is a well-described bidirectional association between the dysfunction of the heart and the kidneys, known as cardiorenal syndrome, whereby dysfunction in one of the organs is associated with dysfunction in the other.[2] There is similarly widespread appreciation of the syndrome of cardiometabolic disease. Excess and dysfunctional adipose tissue (particularly visceral adiposity and other ectopic fat deposition) can cause inflammation, insulin resistance and the emergence of metabolic risk factors and myriad systemic effects, including an increased risk for CVD.[3] Although these syndromes are well recognized, there is growing awareness that metabolic abnormalities play a key pathophysiological role in bidirectional cardiovascular-kidney interactions. In addition, kidney dysfunction is increasingly recognized as a key mediator of the relationship between metabolic risk factors and CVD, particularly heart failure (HF).[4,5] Therefore, rather than simply considering cardiorenal syndrome and cardiometabolic disease as separate entities, it is increasingly clear that we need to consider their overlap as a broader construct of CKM syndrome.

Nearly every major organ system is affected as a consequence of CKM syndrome, with associated clinical challenges including kidney failure,[6] premature cognitive decline,[7,8] metabolic dysfunction–associated steatotic liver disease (previously nonalcoholic fatty liver disease),[9,10] obstructive sleep apnea,[11] and increased risk for cancer.[12,13] However, the greatest clinical impact of CKM syndrome with regard to morbidity and premature mortality is through the disproportionate burden of CVD.[14] CKM syndrome affects vascular integrity, atherogenesis, myocardial function, hemostasis and cardiac conduction. As a result, CKM syndrome is linked to greater likelihood of all phenotypes of CVD, including coronary heart disease, stroke, HF, peripheral artery disease, atrial fibrillation and sudden cardiac death.[15–20]

The public health urgency associated with CKM syndrome is a consequence of the historically high prevalence of obesity and diabetes in both adults and youth, with a disproportionate burden in disenfranchised populations.[21,22] The uneven burden of CKM syndrome in the population is a key driver of CVD disparities.[23] CKM syndrome is also linked to high health care expenditures: Overweight/obesity and downstream comorbid conditions are associated with almost half a trillion dollars in annual direct health care costs and an additional $1.2 trillion in annual indirect costs related to lost economic productivity.[24] However, the greatest clinical consequence of the increased CVD risk in CKM syndrome is a reduction in survival. Higher degrees of obesity are associated with progressively premature mortality, with grade III obesity (body mass index [BMI] 40 to <45 kg/m^2) linked to a median survival reduction of 8 to 10 years.[25] Men and women with diabetes have a 13- to 14-year-shorter life span than their counterparts without diabetes, with earlier onset of diabetes associated with greater survival reductions.[26] Compared with middle-aged individuals who have normal or mildly decreased kidney function (estimated glomerular filtration rate [eGFR] ≥60 mL·min^{-1}·1.73 m^{-2}), those with stage 4 CKD (15–29 mL·min^{-1}·1.73 m^{-2}) have >20-year-shorter life expectancy, with death resulting from CVD being a major competing risk for the development of kidney failure requiring kidney replacement therapies.[27] Albuminuria is also a strong risk predictor for adverse cardiovascular events; however, rates of albuminuria testing remain very low in general practice, even among high-risk groups with long-established recommendations for testing, including those with diabetes and CKD.[28] Moreover, because of the interconnectedness inherent to CKM syndrome, many individuals have combinations of these conditions, with resultant higher mortality rates. For example, in a nationwide sample, although diabetes and CKD were each separately associated with high 10-year mortality rates (7.7% and 11.5%, respectively), the combination of diabetes and CKD was linked to a synergistically higher 10-year mortality rate (31.1%).[29] As a result of the potent risk associations for CKM syndrome, prior continuous declines in CVD mortality rates achieved over 5 decades have recently begun to plateau, with increasing CVD mortality rates seen in some subpopulations.[30]

Although there is a critical need to address CKM health, there is also significant potential for positively influencing CKM-related outcomes. There are now several therapies with multiple beneficial effects on metabolic risk factors, kidney function and the cardiovascular system. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally developed as antidiabetic agents, are now known to prevent kidney failure and to have cardioprotective effects, most notably on HF-related hospitalizations and CVD mortality.[31,32] Glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) not only improve insulin resistance and glycemia but also reduce weight and cause significant reductions in CVD mortality.[33] Renin-angiotensin-aldosterone system (RAAS) inhibitors also have important cardiovascular and kidney benefits.[34–36] The availability of effective approaches to address excess adiposity and related insulin resistance provides the opportunity to address the root cause of a large component of CKM syndrome. It is also necessary to consider social determinants of health (SDOH), both in estimating CKM-related risk and in approaches to management. In addition, the American Heart Association's (AHA's) Life's Essential 8 construct[37] and growing recognition of the need to move beyond subspecialty silos to collaborative interdisciplinary care models can support more holistic patient care approaches to achieve optimal CKM health.

These significant advances in therapeutic approaches have the potential to transform the future of CKM health and to reverse current adverse trends in population-level cardiovascular mortality. However, greater clarity is urgently needed on the identification

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of and care for the patient with CKM. Therefore, in this presidential advisory, we define CKM syndrome, describe a staging construct, discuss approaches for predicting CKM-related outcomes, provide guidance on approaches to prevention and management, and outline a call to action for advancing CKM care. The present advisory is accompanied by a scientific statement detailing the current evidence underlying approaches to CKM health and identifying gaps in our scientific understanding and management of the patient with CKM syndrome.[1] The overarching purpose of these documents is to provide a framework for holistically and equitably improving CKM health in the United States and globally.

DEFINITION OF CKM SYNDROME

A fundamental step in diagnosing and treating patients with CKM syndrome is to comprehensively but precisely define the patient with or at risk for CKM syndrome and its attendant consequences. A key motive underpinning the need for a consensus definition of CKM syndrome is that there is significant heterogeneity of expert opinion as to what constitutes CKM syndrome, to what degree it represents a syndrome or continuum of disease, and the impact of its health-related effects beyond that of its component disorders.

A syndrome is defined as a collection of related signs and symptoms indicating a common underlying pathophysiology rather than a formal diagnosis. Therefore, the term syndrome rather than disease is best applied to CKM, reflecting both the multiple interrelated factors affecting CKM health and the spectrum of severity within the CKM construct with regard to pathology, end-organ damage and risk for CVD events and mortality. A definition of CKM syndrome enables prompt identification of the appropriate patient (including with population-based tools such as electronic medical record screening), assessment of both biological and social determinants of poor CKM health, and classification into a CKM staging rubric with guideline-directed, actionable recommendations for comprehensive care.

The definition of CKM syndrome will help to identify individuals at high risk for CKM morbidity and mortality and to initiate preventive strategies before end-organ damage occurs. From a public health and community-facing perspective, a unifying definition is needed to facilitate communication between the scientific community and community stakeholders and to underscore the importance of taking CKM syndrome into consideration when determining health policy and investment in federally or privately funded research or public health initiatives. Last, it is important that the definition of CKM syndrome integrates contemporary constructs of cardiovascular health (eg, the AHA's Life's Essential 8) and recognizes SDOH and the importance of positive health promotion and preservation across the life course in populations and individuals.

This presidential advisory introduces a consensus definition for CKM syndrome, formed through extensive discussion and evidence-based rationale, from experts with wide-ranging expertise in all of the CKM domains. Henceforth, we have defined CKM syndrome as follows:

- CKM syndrome is a systemic disorder characterized by pathophysiological interactions among metabolic risk factors, CKD, and the cardiovascular system leading to multiorgan dysfunction and a high rate of adverse cardiovascular outcomes. CKM syndrome includes both individuals at risk for CVD due to the presence of metabolic risk factors, CKD, or both and individuals with existing CVD that is potentially related to or complicates metabolic risk factors or CKD. The increased likelihood of CKM syndrome and its adverse outcomes is further influenced by unfavorable conditions for lifestyle and self-care resulting from policies, economics and the environment.

The presidential advisory also provides a more simplified and patient-facing definition of CKM syndrome for use in the lay public:

- CKM syndrome is a health disorder due to connections among heart disease, kidney disease, diabetes and obesity leading to poor health outcomes.

This definition serves as a starting point to define and describe the stages of CKM syndrome, to identify evidence-based best practices for addressing CKM syndrome in clinical practice, and to develop tools to screen and risk-stratify individuals for adverse outcomes linked to CKM syndrome, with resultant prompt initiation of preventive and treatment strategies.

STAGING RATIONALE

Current evidence indicates that CKM syndrome is a progressive condition that commonly begins in early life with biological, social and environmental exposures or pressures leading to the accumulation of excess and dysfunctional adipose tissue,[38,39] with resultant inflammation, oxidative stress and insulin resistance. Excess and dysfunctional adipose tissue frequently progresses to the development of metabolic risk factors (eg, hypertension, hypertriglyceridemia, metabolic syndrome [MetS], type 2 diabetes) and CKD.[40] Over time, these often confluent comorbidities result in the development of subclinical coronary atherosclerosis (reflected by coronary artery calcification) and subclinical abnormalities of myocardial structure and function, as well as progressive declines in kidney function, which predispose to a high risk for clinical CVD, kidney failure, disability and death. It is critical to identify windows for preventive action during the early stages of CKM syndrome, when patients are frequently asymptomatic, and to tailor the aggressiveness of preventive interventions to absolute CVD risk and expected net benefit. Furthermore, interventional studies targeting

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various CKM risk factors suggest that earlier detection and intervention are often associated with greater clinical benefit.

In recognition of the importance of these concepts, this advisory proposes a novel model that classifies CKM syndrome into stages (Figure 1 and Table 1): stage 0, no CKM risk factors present (absence of excess/dysfunctional adiposity, metabolic risk factors, CKD); stage 1, excess adiposity, dysfunctional adiposity, or both, with dysfunctional adiposity defined as hyperglycemia or prediabetes; stage 2, metabolic risk factors, moderate- to high-risk CKD, or both; stage 3, subclinical CVD overlapping with CKM risk factors, very high-risk CKD, or high predicted CVD risk; and stage 4, clinical CVD overlapping with CKM risk factors. Stage 4 is further divided into stages 4a (without kidney failure) and 4b (with kidney failure). The designations of moderate-, high- and very high-risk CKD are defined by the Kidney Disease Improving Global Outcomes (KDIGO) heat map (Figure 2), which creates categories based on combinations of eGFR and albuminuria. The KDIGO classifications of moderate-, high- and very high-risk CKD reflect increasing risk for kidney failure, CVD and all-cause mortality.[41]

The CKM staging model emphasizes the progressive pathophysiology of CKM syndrome, underscores the importance of early detection of CKM-related changes to support prevention efforts, and highlights the stepwise increase in absolute CVD risk associated with later stages, when intensified therapies for patients with CKM syndrome will have the greatest net clinical benefit.

Stage 0: No CKM Risk Factors

Stage 0 is defined as the absence of CKM risk factors with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD. Because the development of CKM risk factors is more common with aging, survey data indicate that stage 0 CKM is most commonly, but not exclusively, encountered among youth and young adults. The focus of stage 0 is primordial prevention, with a goal of preventing the development of CKM risk factors through the achievement and maintenance of ideal cardiovascular health starting in early life.

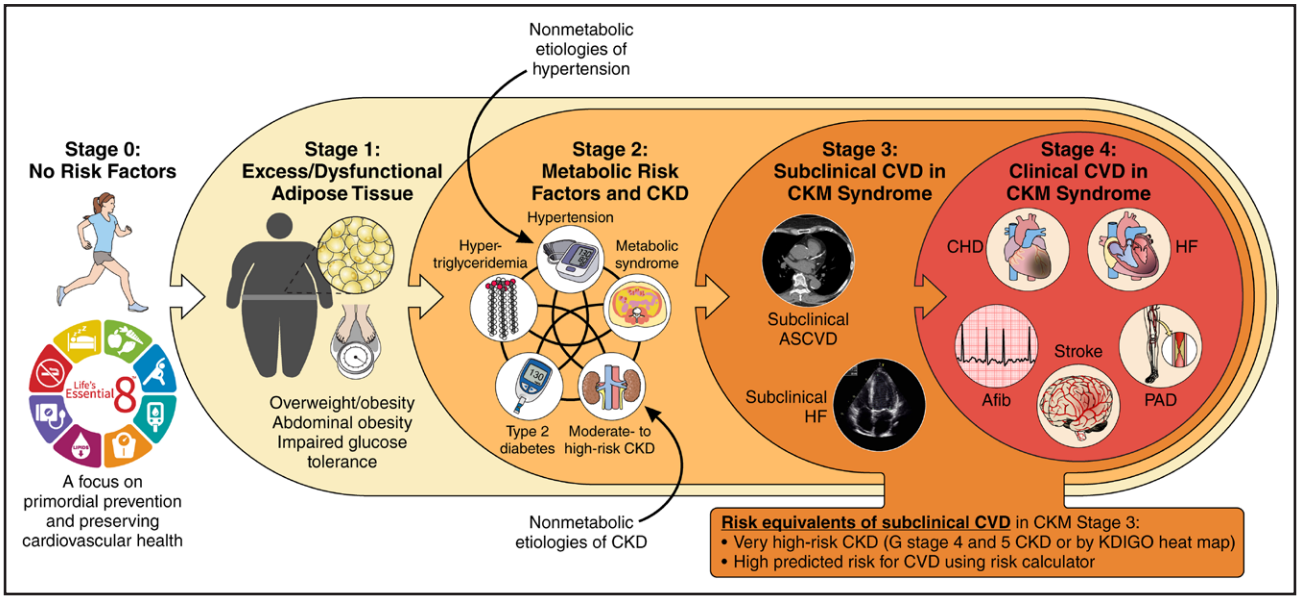
Nonmetabolic etiologies of hypertension
Stage 0: No Risk Factors
Stage 1: Excess/Dysfunctional Adipose Tissue
Stage 2: Metabolic Risk Factors and CKD
Stage 3: Subclinical CVD in CKM Syndrome
Stage 4: Clinical CVD in CKM Syndrome
Hypertension
Hyper-triglyceridemia
Metabolic syndrome
Type 2 diabetes
Moderate- to high-risk CKD
Overweight/obesity
Abdominal obesity
Impaired glucose tolerance
Subclinical ASCVD
Subclinical HF
CHD
HF
Stroke
Afib
PAD
Life's Essential 8
A focus on primordial prevention and preserving cardiovascular health
Nonmetabolic etiologies of CKD
Risk equivalents of subclinical CVD in CKM Stage 3:
• Very high-risk CKD (G stage 4 and 5 CKD or by KDIGO heat map)
• High predicted risk for CVD using risk calculator

Figure 1. Stages of CKM syndrome.
The cardiovascular-kidney-metabolic (CKM) staging construct reflects the progressive pathophysiology and increasing absolute cardiovascular disease (CVD) risk along the spectrum of CKM syndrome. Stage 0 CKM includes individuals with normal weight, normal glucose, normal blood pressure, normal lipids, normal kidney function, and no evidence of subclinical or clinical CVD; the focus in stage 0 CKM is primordial prevention and preserving cardiovascular health. Stage 1 CKM includes individuals with excess adipose tissue, dysfunctional adipose tissue, or both. Excess adiposity is identified by either weight or abdominal obesity, and dysfunctional adipose tissue is reflected by impaired glucose tolerance and hyperglycemia. Stage 2 includes individuals with metabolic risk factors (hypertriglyceridemia, hypertension, metabolic syndrome, or type 2 diabetes), moderate- to high-risk chronic kidney disease (CKD), or both. Although hypertension and CKD are usually downstream of metabolic risk factors, the curved arrows represent individuals with nonmetabolic causes of these conditions; the risk implications and treatment approaches are similar. Stage 3 includes individuals with subclinical CVD with overlapping CKM risk factors (excess/dysfunctional adipose tissue, metabolic risk factors, or CKD) or those with the risk equivalents of very high-risk CKD or high predicted risk using the forthcoming CKM risk calculator. Stage 4 includes individuals with clinical CVD (coronary heart disease, HF, stroke, peripheral artery disease, or atrial fibrillation) overlapping with CKM risk factors. Afib indicates atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; and PAD, peripheral artery disease.

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Table 1. Definitions of CKM Syndrome Stages

CKM syndrome stages	Definition
Stage 0: No CKM risk factors	Individuals with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD
Stage 1: Excess or dysfunctional adiposity	Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD BMI ≥25 kg/m² (or ≥23 kg/m² if Asian ancestry), Waist circumference ≥88/102 cm in women/men (or if Asian ancestry ≥80/90 cm in women/men), or Fasting blood glucose ≥100–124 mg/dL or HbA1c between 5.7% and 6.4%*
Stage 2: Metabolic risk factors and CKD	Individuals with metabolic risk factors (hypertriglyceridemia [≥135 mg/dL], hypertension, MetS,† diabetes), or CKD
Stage 3: Subclinical CVD in CKM	Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Subclinical ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria) Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, hs-troponin T ≥14 ng/L for women and ≥22 ng/L for men, hs-troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with a combination of the 2 indicating highest HF risk. Risk equivalents of subclinical CVD Very high-risk CKD (stage G4 or G5 CKD or very high risk per KDIGO classification) High predicted 10-y CVD risk
Stage 4: Clinical CVD in CKM	Clinical CVD (coronary heart disease, HF, stroke, peripheral artery disease, atrial fibrillation) among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD Stage 4a: no kidney failure Stage 4b: kidney failure present

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CT, computed tomography; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HF, heart failure; hs-troponin, high-sensitivity troponin; KDIGO, Kidney Disease Improving Global Outcomes; MetS, metabolic syndrome; and NT-proBNP; N-terminal pro-B-type natriuretic peptide.

*Individuals with gestational diabetes should receive intensified screening for impaired glucose tolerance after pregnancy.

†MetS is defined by the presence of 3 or more of the following: (1) waist circumference ≥88 cm for women and ≥102 cm for men (≥80 cm for women and ≥90 cm for men if Asian ancestry); (2) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women; (3) triglycerides ≥150 mg/dL; (4) elevated blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg and/or use of antihypertensive medications); and (5) fasting blood glucose ≥100 mg/dL.

Stage 1: Excess or Dysfunctional Adiposity

Stage 1 is defined as having excess weight (BMI ≥25 kg/m^2), abdominal obesity (waist circumference ≥88 cm in women and ≥102 cm in men), or dysfunctional adipose tissue (clinically manifest as impaired glucose tolerance or prediabetes) without the presence of other metabolic risk factors or CKD. Lower anthropometric cut points are advised for Asian populations (BMI ≥23 kg/m^2 and waist circumference ≥80 cm in women or ≥90 cm in men) given their predisposition to developing metabolic abnormalities at lower levels of adiposity.[42] Pathogenetically, the majority of CKM syndrome factors stem from an excess and dysfunction of adipose tissue, particularly visceral and ectopic body fat.[20] Excess visceral adipose tissue, which is frequently accompanied by ectopic fat deposition in normally lean tissues (eg, liver, heart, skeletal muscle, pancreas, kidney), is associated with the development of insulin resistance, systemic inflammation, and oxidative stress that contribute to the development of metabolic risk factors and CKD. A consequence of dysfunctional adipose tissue is impaired glucose tolerance and subsequent hyperglycemia, which increase the likelihood of metabolic risk factors and can occur even in those with normal BMI. One group deserving of particular focus is women with a history of gestational diabetes, who are at marked risk of diabetes and should be monitored for impaired glucose tolerance after pregnancy.[43] Enhancing the recognition and management of excess and dysfunctional adiposity is critical for the prevention of metabolic risk factors and CKD.[44]

Stage 2: Metabolic Risk Factors and Kidney Disease

Stage 2 of CKM syndrome is defined as the presence of metabolic risk factors (hypertriglyceridemia [≥135 mg/dL], hypertension [stages 1 and 2], MetS, diabetes), moderate- to high-risk CKD, or both. Pathophysiologically, hypertriglyceridemia, MetS and type 2 diabetes are almost entirely downstream of excess or dysfunctional adipose tissue.[45] Although most hypertension is related to adiposity and other metabolic risk factors,[46] it also occurs in the absence of these conditions, but therapeutic approaches and goals are typically similar regardless of cause. Similarly, CKD, defined by low eGFR or albuminuria that persists for ≥3 months, most often occurs secondary to metabolic risk factors, especially hypertension and diabetes.[47] Even when CKD occurs from other causes, in the absence of hypertension and diabetes, the impact on CVD risk and the therapeutic approaches to prevent kidney function decline are largely similar. There are considerable pathophysiological interrelationships among stage 2 CKM components, with MetS predisposing to diabetes,[48] diabetes and hypertension leading to CKD, and CKD leading to hypertension.[49,50] The presence of MetS is associated with pathophysiological changes, including endothelial function, increased inflammation and prothrombotic changes; emphasizes the interrelatedness of stage 2 CKM conditions; and underscores the importance of lifestyle modification to address measured and unmeasured MetS components. In stage 2 CKM, there is a focus on lifestyle and pharmacological intervention for modifiable risk factors to prevent the development of CVD and kidney failure.

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CKD is classified based on:
Cause (C)*
GFR (G)†
Albuminuria (A)†

GFR categories (mL/min per 1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer† 3	Treat and refer† 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
High risk
Moderately increased risk
Very high risk

Figure 2. KDIGO heat map for CKD classification.
*Cause refers to the cause of CKD as ascertained by the clinician. Most patients who fit into the cardiovascular-kidney-metabolic (CKM) staging framework will have CKD attributable to diabetes, hypertension, and other metabolic risk factors. However, pharmacotherapies such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and sodium-glucose cotransporter-2 inhibitors have demonstrated kidney and cardiovascular benefits in trials for patients with CKD resulting from either metabolic risk factors or other causes (eg, some glomerulopathies). Therefore, the CKM staging framework is relevant for almost all patients with CKD. †Clinicians may wish to discuss with their nephrology service, depending on local practice patterns on monitoring or referring. CKD indicates chronic kidney disease; and GFR, glomerular filtration rate.

Stage 3: Subclinical CVD in CKM Syndrome

Stage 3 is defined as subclinical CVD among individuals with excess/dysfunctional adiposity, metabolic risk factors, or CKD. This includes imaging markers of subclinical atherosclerotic CVD (ASCVD; most frequently an increased coronary artery calcium [CAC] score on cardiac computed tomography but also potentially reflected by nonobstructive coronary artery disease on coronary angiography or by subclinical peripheral artery disease) or subclinical HF, ascertained through either elevation in cardiac biomarkers (eg, BNP [B-type natriuretic peptide], NT-proBNP [N-terminal pro-B-type natriuretic peptide], high-sensitivity cardiac troponins) or abnormal cardiovascular structure or function on myocardial imaging in the absence of clinical symptoms. The presence of subclinical CVD has been associated with an increased absolute risk of future CVD and, in some cases, an increased risk of mortality.[51–54] Given the focus on high absolute CVD risk, stage 3 CKM also includes individuals with high predicted CVD risk through the CKM risk algorithm or with very high-risk CKD as per the KDIGO heat map, which indicates markedly elevated risk for CVD, kidney failure and mortality.

Stage 3 CKM is a high-risk phenotype in which preventive therapies can delay or halt progression to clinical disease and will confer the greatest net clinical benefit given the higher absolute baseline risk than earlier CKM stages. By providing objective evidence of early

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end-organ damage, this approach may also facilitate clinician-patient communication concerning preventive therapeutic strategies.

Stage 4: CVD in CKM Syndrome With and Without Kidney Failure

Stage 4 CKM syndrome is defined as clinical CVD among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD. There are bidirectional relationships between CKM factors and the entire spectrum of CVD, including ischemic heart disease,[55] cerebrovascular and peripheral artery disease,[56] arrhythmias (atrial fibrillation),[57] and HF.[20] In particular, a disproportionate risk of HF with preserved ejection fraction compared with HF with reduced ejection fraction (HFrEF) is notable with obesity and physical inactivity.[58] The emphasis in stage 4 CKM is on unique management considerations for CVD in the context of CKM conditions. Stage 4 is divided into individuals without kidney failure (4a) and those with kidney failure (4b). The reason is that there are unique management considerations, particularly for HF, ischemic heart disease and atrial fibrillation, for patients with kidney failure superimposed on CVD. Furthermore, individuals with CVD and a confluence of multiple CKM factors are a group with a particularly high risk for recurrent CVD events and mortality for whom coordinated interdisciplinary care is imperative.

Risk-Enhancing Factors

In addition to the progression in pathophysiology and risk represented by the CKM staging construct, several other factors enhance the likelihood of progression along CKM stages, with associated increased risk for CVD and kidney failure. These include belonging to high-risk demographic groups (individuals of South Asian ancestry and those with low socioeconomic status) and having a family history of diabetes or kidney failure, sleep disorders, mental health disorders, chronic inflammatory conditions, sex-specific risk enhancers (including premature menopausal transition, adverse pregnancy outcomes and polycystic ovarian disease), and higher adverse SDOH burden (Table 2).

Table 2. Risk-Enhancing Factors for CKM Syndrome*

Chronic inflammatory conditions (eg, psoriasis, RA, lupus, HIV/AIDS)
High-risk demographic groups (eg, South Asian ancestry, lower socioeconomic status)
High burden of adverse SDOH
Mental health disorders (eg, depression and anxiety)
Sleep disorders (eg, obstructive sleep apnea)
Sex-specific risk enhancers (beyond gestational diabetes consideration in stage 1)
History of premature menopause (age <40 y)
History of adverse pregnancy outcomes (eg, hypertensive disorders of pregnancy, preterm birth, small for gestational age)
Polycystic ovarian syndrome
Erectile dysfunction
Elevated high-sensitivity C-reactive protein (≥2.0 mg/L if measured)
Family history of kidney failure; family history of diabetes

CKM indicates cardiovascular-kidney-metabolic; RA, rheumatoid arthritis; and SDOH, social determinants of health.

*These factors increase the likelihood of progression along CKM stages with associated risk for cardiovascular disease and kidney failure.

SCREENING

The CKM staging approach facilitates identifying individuals at different levels of syndromic severity, thereby providing windows for preventive action to halt or reverse disease progression. Within the CKM staging construct, there is particular focus on detecting individuals in the preclinical phase, with the goal of delaying or averting the onset of clinical CVD and kidney failure. To appropriately categorize largely asymptomatic individuals in clinical settings into CKM stages, there is a need for active screening within the population. Screening tests should be highly accurate and reproducible and readily accessible at the population level. It is also critical that the results of screening tests directly influence approaches to care. In addition, some diagnostic tests should be targeted to high-yield populations such as assessments for subclinical CVD in older and higher-risk subgroups.

CKM-related screening falls into 2 primary categories: screening for biological factors and screening for SDOH. The biological factors include screening for metabolic risk factors and measures of kidney function, in addition to diagnostic testing for subclinical atherosclerosis and cardiac dysfunction in select clinical circumstances. The identification of each of these factors directly informs the selection and intensity of interventions to prevent CVD and progressive CKD or influences the management of patients with prevalent CVD. Screening for SDOH characterizes social and structural barriers to healthy lifestyle, self-care, health care access, and disease prevention and management that powerfully influence the identification of CKM risk factors and outcomes in CKM syndrome. Integrating SDOH into the holistic approach to CKM care will enhance the real-world effectiveness of therapeutic approaches and promote health equity.

Early Life Assessments

CVD develops across the life span from conception to later adulthood, and exposure to risk factors for disease development begins even before conception.[38] In utero exposures to maternal obesity and hypertension affect offspring cardiometabolic risk factors through the process of genomic imprinting.[59,60] Increased consumption

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of calorie-rich foods and beverages, less physical activity, and more sedentary behavior, driven by multilevel SDOH, have contributed to the growing and historic prevalence of obesity and related cardiometabolic risk factors among youth.[61] CKD in pediatric populations is linked to the development of CVD risk factors and to excess CVD mortality; risk factor modification, particularly hypertension control, is linked to slower CKD progression.[62,63] Risk factors in youth are linked to early cardiovascular abnormalities and frequently track into adulthood.[64,65] Nonetheless, there is conflicting guidance from major organizations on the utility of screening for risk factors in youth.

The consensus of this presidential advisory aligns with the American Academy of Pediatrics approach for screening in pediatric populations[66] (Table 3). This includes annual screening for overweight and obesity and blood pressure assessments at each clinic visit beginning at 3 years of age, as well as at least annual assessments of mental and behavioral health. A lipid panel should be checked between 9 and 11 years of age and again between 17 and 21 years of age, with additional assessment of impaired glucose tolerance (by fasting glucose, oral glucose tolerance test, or hemoglobin A1c [HbA1c]) and alanine aminotransferase in those with overweight or obesity who are at higher risk for type 2 diabetes or metabolic dysfunction–associated steatotic liver disease. This approach will support CKM staging and the related targeted preventive action in children and adults.

Assessments for CKM Risk Factors Among Adults

Enhanced screening is also needed among adults to improve the identification of asymptomatic CKM risk factors, to support CKM staging, and to enhance targeted prevention efforts. The measurement of both BMI and waist circumference annually is suggested to fully characterize adiposity-related risk (Table 3). For individuals in stage 2 CKM or higher, who already have some metabolic risk factors, we advise annual assessment of MetS components: blood pressure, triglycerides, high-density lipoprotein cholesterol and hyperglycemia. Lipid measurements do not require fasting. Hyperglycemia can be assessed with fasting glucose or HbA1c; the latter does not require fasting. For those in stage 1 CKM, who are at high risk for developing metabolic risk factors, we advise screening for MetS components every 2 to 3 years. We additionally advise screening for MetS components every 3 to 5 years in adults in stage 0 CKM; such an approach supports equity in the identification of CKM risk factors. For those individuals with metabolic risk factors, screening for metabolic dysfunction–associated steatotic liver disease every 1 to 2 years is advised in current guidelines.[67]

Among adults with stage 2 CKM and higher, we advise annual urine albumin-creatinine ratio (UACR) measurements along with eGFR estimation using serum creatine or cystatin C to allow accurate KDIGO staging and the best risk prognostication in relation to CKD. More frequent screening is indicated for those with higher KDIGO risk as per current guidelines. The presence of subclinical ASCVD or HF or a risk equivalent in stage 3 CKM indicates high absolute risk warranting consideration

Table 3. Screening Approaches for CKM Syndrome

Period	Screening approach
Early life (<21 y)	Screening for overweight and obesity using sex- and age-specific CDC growth charts: annually Blood pressure assessment (stronger evidence/recommendation for those with CKM factors): starting at age 3 y, annually for children with no risk factors; at every health encounter for children with overweight/obesity, diabetes, kidney disease, or structural heart disease Mental and behavioral health, SDOH screening for all children Fasting lipid panel recommended: once between 9 and 11 y of age and then again between 17 and 21 y of age Screening is advised beginning at 2 y of age if a family history is suggestive of either early CVD or significant primary hypercholesterolemia. Additionally check FPG/OGTT/HbA1c, ALT: starting at 9-11 y of age If normal, may repeat every 2–3 y for all children with obesity If normal, may repeat every 2–3 y for children with overweight if additional risk factors present (family history of obesity-related diseases, elevated blood pressure or lipid levels, tobacco use)
Adulthood (≥21 y)	Screening for social determinants of health (see Table 4) Measurement of BMI and waist circumference: annually Screening for MetS components (elevated blood pressure, elevated triglycerides, low HDL cholesterol, and hyperglycemia) Annually for those with stage 2 CKM Every 2–3 y for those with stage 1 CKM or history of gestational diabetes Every 3–5 y for those with stage 0 CKM Screening for advanced liver fibrosis related to MASLD every 1–2 y for individuals with diabetes, prediabetes, or ≥2 metabolic risk factors using the FIB-4 index Assessment of UACR along with serum creatinine/cystatin C for accurate KDIGO staging Annually for those with stage 2 CKM or higher More frequently for those with higher KDIGO risk Coronary artery calcium screening reasonable in those with intermediate 10-y ASCVD risk to guide intensification of preventive therapies Subclinical HF screening with echocardiogram and/or cardiac biomarkers likely based on age/comorbidities/risk score but not yet defined

ALT indicates alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; FIB-4, Fibrosis-4; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; MASLD, metabolic dysfunction–associated steatotic liver disease; MetS, metabolic syndrome; OGTT, oral glucose tolerance test; SDOH, social determinants of health; and UACR, urine albumin-creatinine ratio.

(FIB-4=(age×AST)/(platelet count×√ALT).

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for intensified lifestyle and pharmacological intervention. As per the AHA/American College of Cardiology primary prevention guideline[67a] and cholesterol management guideline,[67b] measurement of CAC is reasonable in those with borderline or intermediate ASCVD risk per 10-year risk calculators to guide the use of statin therapy for ASCVD prevention. More recent guidance from the American Diabetes Association suggests that diagnostic testing for subclinical HF should likely be based on age and comorbidity profile,[68] but the optimal strategy for identifying subclinical HF in the population, reflecting both clinical benefit and cost-effectiveness, is still being defined.

SDOH Screening

SDOH, or the economic, social, environmental, and psychosocial factors that affect health outcomes over the life course, have a prominent impact on CKM health.[69] SDOH influence CKD development, diagnosis and outcomes.[70,71] Moreover, adverse SDOH are associated with disparities in cardiovascular health behaviors, including physical activity, dietary intake and nutrition, incident obesity and diabetes and subsequent complications from these conditions.[20,23,72] Ultimately, adverse individual- and neighborhood-level SDOH have downstream consequences for cardiovascular events and cardiovascular and all-cause mortality.[69]

Recent work highlights the importance of understanding specific social needs related to SDOH for CKM prevention and treatment. Numerous screening tools exist to survey financial strain (ie, food and housing insecurity, transportation and utility needs, health care access), education/literacy, personal safety and perceived need for assistance in addressing social needs (Table 4).[73–80] Some survey instruments, including the Oregon Community Health Information Network[77] and the Centers for Medicare & Medicaid Services tools,[74] assess health behaviors affected by SDOH (ie, physical activity and tobacco or alcohol use). Most available screening tools include mental health measures to assess depression, social isolation, or stress. The Protocol for Responding to and Assessing Patients' Assets, Risks and Experiences is a unique survey instrument because it also assesses refugee status and prior incarceration in addition to other, more traditional SDOH.[76] The Health Leads tool specifically addresses health literacy.[73] The American Academy of Family Physicians[75] and Health Leads[73] tools can be self-administered. Last, the Oregon Community Health Information Network tool was created for use in electronic health records of community health centers,[77] whereas the Health Leads and Protocol for Responding to and Assessing Patients' Assets, Risks and Experiences tools have been developed with steps for incorporation into the clinical care workflow. Although most screening tools have been created for adult patients, specific screening

Table 4. SDOH Screening Tools

Screening tool	Domains assessed by the screening tool
Health Leads[73]	Essential domains: food insecurity, housing instability, utility needs, financial resource strain, transportation challenges, exposure to violence, sociodemographic information Optional domains: childcare, education, health literacy, employment, health behaviors, social isolation and supports, behavioral/mental health
Centers for Medicare & Medicaid Innovation: Accountable Health Communities Health-Related Social Needs Screening Tool[74]	Core domains: housing instability, food insecurity, transportation problems, utility help needs, interpersonal safety Supplemental domains: financial strain, employment, family and community support, education, physical activity, substance use, mental health, disabilities
AAFP: The EveryONE Project[75]	Housing, food, transportation, utilities, childcare, employment, education, finances, personal safety
PRAPARE Implementation and Action Toolkit[76]	Personal characteristics: race, ethnicity, farmworker status, language preference, veteran status Family and home: housing status and stability, neighborhood Money and resources: education, employment, insurance status, income, material security, transportation needs Social and emotional health: social integration and support, stress Other measures: incarceration history, safety, refugee status, domestic violence
OCHIN: Social Determinants of Health Electronic Health Record Tools in Community Health Centers[77]	Housing insecurity, food insecurity, education, financial resource strain, alcohol use, race, ethnicity, tobacco use and exposure, depression, exposure to violence, physical inactivity, social isolation, stress
SEEK PSQ[78]	Economic stability: food insufficiency Health and health care: smoke alarm needed, contact information for poison control needed Family context: parental intimate partner violence, parental depression, parental stress, parental substance or alcohol use disorder, tobacco use within home, gun in home, help with childcare when needed
IHELP Screening Tool[79]	Economic stability: food insufficiency, housing instability Education: concerns about child's education needs Health and health care: concerns about child's health insurance Neighborhood environment: concerns about physical conditions of housing Family context: violence in the household
WE CARE Screening Tool[80]	Economic stability: food insufficiency, housing instability, difficulty paying bills, parental employment Education: parental education, lack of childcare Family context: intimate partner violence in household, parental depression symptoms, alcohol or substance use disorder in household

AAFP indicates American Academy of Family Physicians; IHELP, Income, Housing, Education, Literacy, and Personal Safety; OCHIN, Oregon Community Health Information Network; PRAPARE, Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences; SDOH, social determinants of health; SEEK PSQ, Safe Environment for Every Kid Parent Screening Questionnaire; and WE CARE, Well Child Care, Evaluation, Community Resources, Advocacy, Referral, Education.

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tools have been developed to assess the unique social needs of caregivers of pediatric patients. For instance, the Safe Environment for Every Kid Parent Screening Questionnaire,[78] the Well Child Care, Evaluation, Community Resources, Advocacy, Referral, Education,[79] and the Income, Housing, Education, Literacy, and Personal Safety[80] screening tools were developed to screen caregivers for SDOH among pediatric populations, have been assessed for validity and reliability, and provide unique information on SDOH among pediatric patients such as contextual factors affecting the household (ie, violence or safety within the home).[81]

Interventions based on SDOH screening have resulted in temporal reductions in social needs.[82] A limited number of interventions have examined health outcomes in the setting of addressing social needs, and few studies have shown improvement in CKM-related factors.[82] For instance, obtaining resources for social needs related to food, housing, medication and transportation after screening was associated with reductions in blood pressure and low-density lipoprotein (LDL) cholesterol but not HbA1c.[83] Assistance provided on the basis of the Accountable Health Communities Health-Related Social Needs Screening Tool from the Centers for Medicare & Medicaid was associated with a reduction in emergency room visits.[84] Other interventions have shown higher smoking cessation rates or greater fruit and vegetable consumption for those who gained resources to address social needs.[82] The 2023 Healthcare Effectiveness Data and Information Set performance measures put forward by Centers for Medicare & Medicaid to track quality improvements for health care plans require reporting of screening and a 1-month intervention on food and housing insecurity and transportation.[85] Moreover, the requirement for federal tax–exempt hospitals to produce a Community Health Needs Assessment every 3 years allows these hospitals to report progress in screening and addressing social needs related to SDOH in their patient populations.[86] Overall, these requirements provide much-needed opportunities for future longitudinal studies to assess temporal trends in social needs among diverse populations and the impact of interventions addressing dynamic changes in social needs on CKM-related outcomes.[87] It is important that future work identify social need interventions to improve CKM health that are effective in resource-limited settings. Effective interventions should be identified for geographic areas where structural racism and other adverse SDOH serve as barriers to health care and healthy behaviors (ie, food deserts)[72] without stigmatizing patients or adding undue clinician burden.[82]

RISK PREDICTION

The approach to preventing CVD events in CKM syndrome will be aided by the development of a new CKM risk prediction algorithm.[88] Key principles for consideration in enhancing prediction efforts in relation to CKM syndrome are detailed in the following sections.

Importance of Predicting Multiple Outcomes (ASCVD, HF and CKD)

Multivariable risk prediction equations have been a cornerstone of ASCVD prevention strategies for >2 decades. Development, validation and implementation of risk prediction tools for ASCVD have guided the widely accepted paradigm of risk-based prevention whereby the intensity of the prevention efforts is matched to the absolute risk of the individual. However, risk-based prevention has been applied primarily to ASCVD to date and has not been broadly implemented in clinical practice for other outcomes such as HF and CKD. Given the rise in morbidity and mortality associated with HF and CKD, incorporating these outcomes into a risk-based approach to prevention is needed to promote CKM health and to improve outcomes. A critical first step is thus the development and evaluation of accurate risk prediction models that quantify the absolute risk of developing any CVD event and its components of interest: ASCVD and HF.

Current guidelines recommend the use of multivariable risk prediction equations for the prevention of both ASCVD and HF. The 2019 AHA/American College of Cardiology guideline for the primary prevention of CVD provide a Class of Recommendation 1, Level of Evidence B-NR for the calculation of 10-year risk of ASCVD with the Pooled Cohort Equations.[67a] The 2022 American College of Cardiology/AHA/Heart Failure Society of America guidelines for the management of HF included for the first time a Class of Recommendation 2a, Level of Evidence B-NR to consider validated multivariable scores to estimate the risk of incident HF.[90] It is well established that the risk factors for both ASCVD and HF overlap, and individuals with multiple risk factors have a higher absolute risk of events.[91] However, a single multivariable risk tool that quantifies risk for CVD and its components (ASCVD and HF) that is accurate, is generalizable for a diverse primary prevention population, and has been well validated is needed. Although other cardiovascular subtypes may be of interest for risk prediction (eg, peripheral artery disease, atrial fibrillation), they have not been prioritized given the challenges in their diagnosis and adjudication and a lack of targeted therapeutic strategies for their prevention.

In addition to the current narrow focus on individual CVD subtypes, existing risk prediction equations for both ASCVD and HF have several other limitations. These include derivation in samples of only White and Black adults who are not representative of the general US population; use of historical data when exposure to risk factors and treatments differed from that in the contemporary era; limited outcome data from racial and ethnic populations who are traditionally underrepresented in clinical studies and trials; lack of inclusion of younger

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adults 18 to 39 years of age; and the absence of SDOH and kidney health markers as predictors. Although the 2019 primary prevention guidelines included CKD as a risk-enhancing factor on the basis of the robust evidence base for the dose-dependent association of kidney function and CVD, markers of kidney function (eg, albuminuria or eGFR) were not incorporated into the Pooled Cohort Equations because of a lack of availability in the derivation samples used. Other investigations have incorporated kidney measures and demonstrated their predictive utility for ASCVD and HF in the general population and among people with CKD.

Therefore, the ideal CVD risk prediction equation would be derived and validated in a sample that closely reflects a contemporary, primary prevention population with racial and ethnic, socioeconomic and geographic diversity; incorporates predictors that are relevant to the CKM at-risk stages that are routinely available in the primary care setting for ease of implementation in clinical care; includes both incident ASCVD and HF as outcomes; and spans a wide age range for relevance across the life course. Furthermore, it is desirable to have the option for adding predictors beyond a core minimal set when available and clinically relevant and to integrate risk prediction into electronic medical records. This would then allow a more accurate assessment of overall risk, optimally inform clinician-patient discussions and guide preventive measures.

Potential to Guide Therapeutic Choices in At-Risk Populations (Particular Focus on GLP-1RAs and SGTL2 Inhibitors)

After accurate and reliable quantification of the absolute risk of CVD, translation and implementation into clinical care are needed to improve outcomes. Risk communication should be paired with evidence-based interventions that subsequently reduce risk. Although the available evidence base for HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors, or statins, is the richest, the emergence of novel therapies that also reduce risk for CVD through lipid lowering (eg, PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitor, PCSK9 siRNA) or alternative pathways (eg, GLP-1RAs and SGLT2 inhibitors) offers new opportunities to integrate risk assessment to guide selection or to prioritize different pharmacotherapies for patients with CKM syndrome.

Contemporary guidelines recommend the initiation of statin therapy for primary prevention of ASCVD according to an individual's 10-year absolute risk as calculated by Pooled Cohort Equations. However, absolute risk thresholds based on absolute risk for overall CVD (both ASCVD and HF) and tailored for each novel therapy still need to be defined. For example, if an individual at risk for CVD in CKM syndrome has a relatively higher risk for HF than ASCVD, this may inform a strategy to prioritize SGLT2 inhibitors when data are robust for the prevention of incident HF among patients with diabetes or CKD. In contrast, if an individual has a relatively higher risk for ASCVD compared with HF, this may inform a strategy to prioritize GLP-1RAs because these therapies have demonstrated a reduction of ASCVD risk. Further data are needed from clinical trials that examine the absolute and relative risk reduction for any CVD event (and separately for ASCVD and HF) for each therapy. In addition to risk reduction, estimation of net benefit for specific therapies, which integrates the potential benefits and harms of a treatment to allow direct comparison of both, can further personalize clinician-patient discussions. The use of an individualized approach to 10-year net benefit for lipid-lowering therapy decisions has been demonstrated to have the potential to prevent more cardiovascular events than the estimation of absolute risk alone. Future studies that model long-term or 30-year benefit are also needed because the absolute benefit of therapies is likely to be underestimated when a limited time scale of 10 years is used, as has been demonstrated for statins.

Emphasis on the Relationship Between Kidney Health and Cardiovascular Health

Kidney health is intricately connected with cardiovascular health, with greater risk for CVD among individuals with impaired kidney function in a dose-dependent manner based on severity of impairment. Therefore, the prediction of kidney function decline or kidney failure has powerful cardiovascular implications. Furthermore, the availability of therapies that prevent decline of kidney function such as angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), SGLT2 inhibitors, and nonsteroidal mineralocorticoid antagonists highlights the importance of risk-based strategies that prioritize both kidney and cardiovascular health. Several risk prediction equations for the development of kidney function decline exist, can inform clinical management, and could facilitate future prevention trials by allowing improved identification and inclusion of individuals at various stages of CKM syndrome.

APPROACH TO CKM PREVENTION AND MANAGEMENT

The approaches to prevention and management across the different stages of CKM syndrome were developed by the CKM Health Scientific Advisory Group after extensive review of the literature and a crosswalk of major clinical guidelines, as described in the accompanying CKM syndrome scientific statement.[1] After achievement of internal consensus within the Scientific Advisory Group, additional external consensus was achieved through presentation to a multidisciplinary group of experts with

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subsequent refinement. The following figures and text describe related suggestions for the care for patients across the spectrum of CKM syndrome. Algorithms for stage 0 through 3 CKM focus on the prevention of CVD events (Figure 3); algorithms for stage 4 CKM focus on CVD management in the context of CKM factors (Figure 4).

Overarching Considerations

Across all stages of CKM syndrome, interdisciplinary care and incorporation of SDOH into the care model are overarching considerations for CKM prevention and management, as shown in the algorithms (Figures 3 and 4).

Interdisciplinary Care

To reduce fragmented care for patients with CKM syndrome with multiorgan disease and to enhance adherence to guidance for holistic CKM care, we propose value- and volume-based approaches to interdisciplinary care (Table 5). A multidisciplinary CKM team is suggested to provide protocolized guidance in conjunction

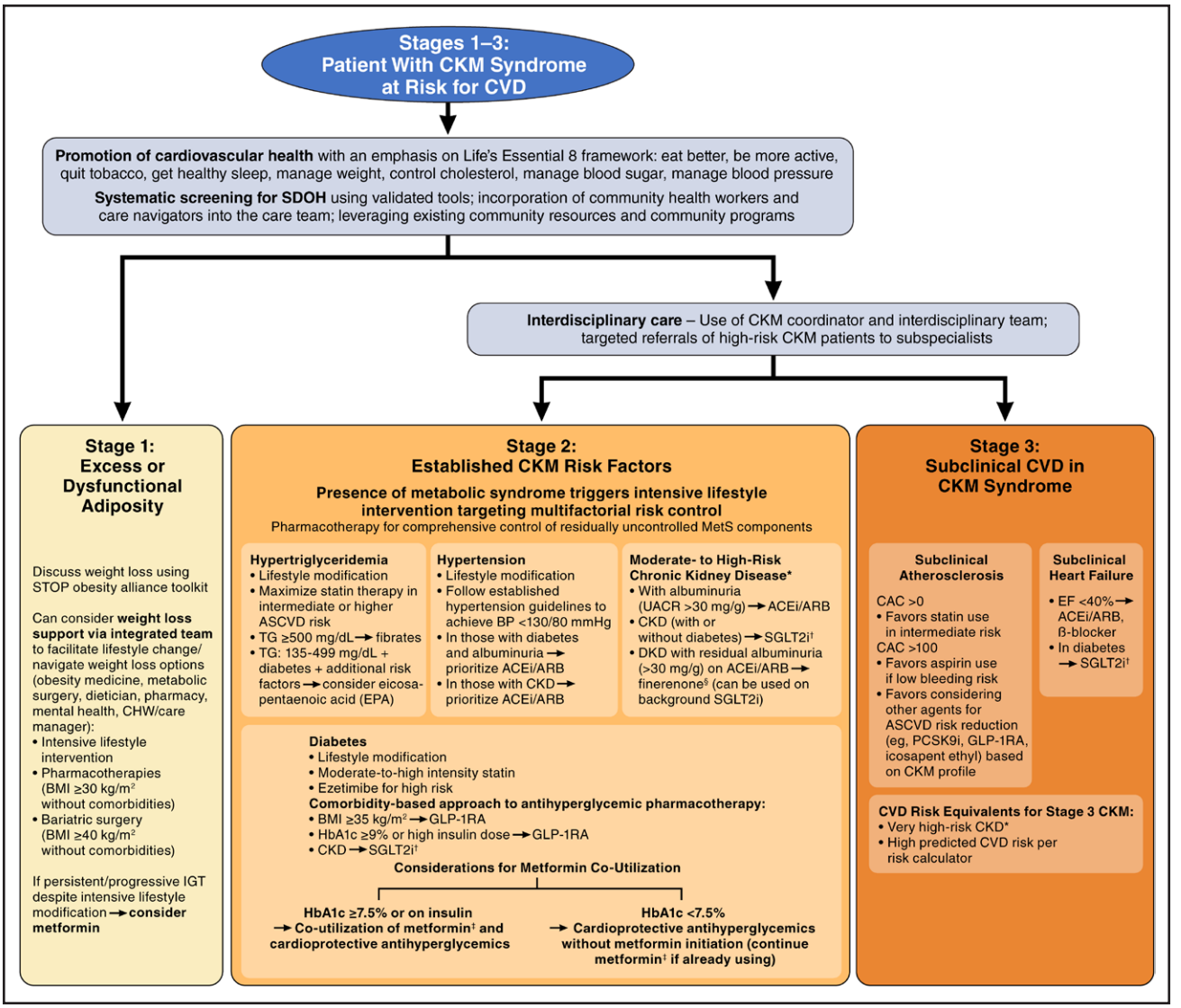

Figure 3. Algorithm for the management of patients with CKM syndrome Stages 1-3.

*Per Kidney Disease Improving Global Outcomes heat map. †SGLT2i can be safely initiated for patients with estimated glomerular filtration rate (eGFR) ≥20 mL·min^{-1}·1.73 m^{-2}. ‡Metformin can be also be used in patients with eGFR ≥30 mL·min^{-1}·1.73 m^{-2}. §Finerenone can likely be initiated on background SGLT2i for those with eGFR >25 mL·min^{-1}·1.73 m^{-2} and potassium <5 mEq/L. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; CHD, coronary heart disease; CHW, community health worker; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes; EF, ejection fraction; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; HF, heart failure; IGT, impaired glucose tolerance; MetS, metabolic syndrome; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; $P2Y_{12}$i, $P2Y_{12}$ inhibitor; SDOH, social determinants of health; SGLT2i, sodium-glucose transport protein 2 inhibitors; STOP, Strategies to Overcome and Prevent; TG, triglycerides; and UACR, urine albumin-creatinine ratio.

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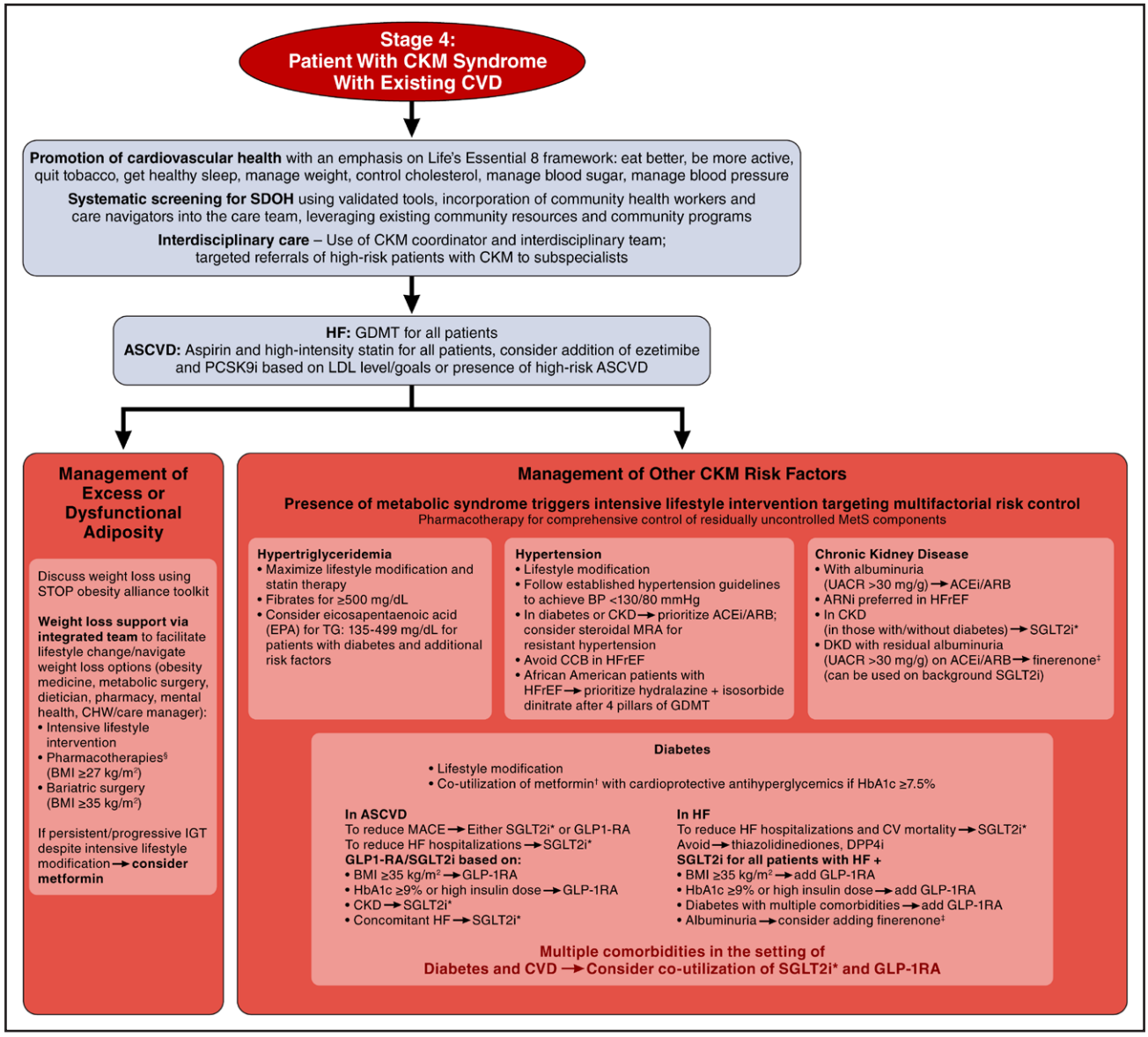
Stage 4:
Patient With CKM Syndrome With Existing CVD
Promotion of cardiovascular health with an emphasis on Life's Essential 8 framework: eat better, be more active, quit tobacco, get healthy sleep, manage weight, control cholesterol, manage blood sugar, manage blood pressure
Systematic screening for SDOH using validated tools, incorporation of community health workers and care navigators into the care team, leveraging existing community resources and community programs
Interdisciplinary care – Use of CKM coordinator and interdisciplinary team; targeted referrals of high-risk patients with CKM to subspecialists
HF: GDMT for all patients
ASCVD: Aspirin and high-intensity statin for all patients, consider addition of ezetimibe and PCSK9i based on LDL level/goals or presence of high-risk ASCVD
Management of Excess or Dysfunctional Adiposity
Discuss weight loss using STOP obesity alliance toolkit
Weight loss support via integrated team to facilitate lifestyle change/navigate weight loss options (obesity medicine, metabolic surgery, dietician, pharmacy, mental health, CHW/care manager):
• Intensive lifestyle intervention
• Pharmacotherapies§ (BMI ≥27 kg/m²)
• Bariatric surgery (BMI ≥35 kg/m²)
If persistent/progressive IGT despite intensive lifestyle modification → consider metformin
Management of Other CKM Risk Factors
Presence of metabolic syndrome triggers intensive lifestyle intervention targeting multifactorial risk control
Pharmacotherapy for comprehensive control of residually uncontrolled MetS components
Hypertriglyceridemia
• Maximize lifestyle modification and statin therapy
• Fibrates for ≥500 mg/dL
• Consider eicosapentaenoic acid (EPA) for TG: 135-499 mg/dL for patients with diabetes and additional risk factors
Hypertension
• Lifestyle modification
• Follow established hypertension guidelines to achieve BP <130/80 mmHg
• In diabetes or CKD → prioritize ACEi/ARB; consider steroidal MRA for resistant hypertension
• Avoid CCB in HFrEF
• African American patients with HFrEF → prioritize hydralazine + isosorbide dinitrate after 4 pillars of GDMT
Chronic Kidney Disease
• With albuminuria (UACR >30 mg/g) → ACEi/ARB
• ARNi preferred in HFrEF
• In CKD (in those with/without diabetes) → SGLT2i*
• DKD with residual albuminuria (UACR >30 mg/g) on ACEi/ARB → finerenone‡ (can be used on background SGLT2i)
Diabetes
• Lifestyle modification
• Co-utilization of metformin† with cardioprotective antihyperglycemics if HbA1c ≥7.5%
In ASCVD
To reduce MACE → Either SGLT2i* or GLP1-RA
To reduce HF hospitalizations → SGLT2i*
GLP1-RA/SGLT2i based on:
• BMI ≥35 kg/m² → GLP-1RA
• HbA1c ≥9% or high insulin dose → GLP-1RA
• CKD → SGLT2i*
• Concomitant HF → SGLT2i*
In HF
To reduce HF hospitalizations and CV mortality → SGLT2i*
Avoid → thiazolidinediones, DPP4i
SGLT2i for all patients with HF +
• BMI ≥35 kg/m² → add GLP-1RA
• HbA1c ≥9% or high insulin dose → add GLP-1RA
• Diabetes with multiple comorbidities → add GLP-1RA
• Albuminuria → consider adding finerenone‡
Multiple comorbidities in the setting of Diabetes and CVD → Consider co-utilization of SGLT2i* and GLP-1RA

Figure 4. Algorithm for the management of patients with CKM syndrome Stage 4.
*SGLT2i can be safely initiated for patients with estimated glomerular filtration rate (eGFR) ≥20 mL·min^{-1}·1.73 m^{-2}. †Metformin can be also be used in patients with eGFR ≥30 mL·min^{-1}·1.73 m^{-2} and without unstable or decompensated HF. ‡Finerenone can likely be initiated on background SGLT2i for those with eGFR >25 mL·min^{-1}·1.73 m^{-2} and potassium <5 mEq/L. §Pending the full results of the SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity), high-dose GLP-1RA may become frontline therapy in patients with obesity and established CVD. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; BMI, body mass index; CCB, calcium channel blocker; CHD, coronary heart disease; CHW, community health worker; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes; DPP4i, dipeptidyl peptidase 4 inhibitor; EF, ejection fraction; GDMT, guideline-directed medical therapy; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; MetS, metabolic syndrome; MRA, mineralocorticoid receptor antagonist; $P2Y_{12}$i, $P2Y_{12}$ inhibitor; SDOH, social determinants of health; SGLT2i, sodium-glucose transport protein 2 inhibitors; STOP, Strategies to Overcome and Prevent; TG, triglycerides; and UACR, urine albumin-creatinine ratio.

with primary care clinicians for the care of the patient with ≥2 overlapping CKM conditions (diabetes, CKD and advanced subclinical/clinical CVD) to support a value-based approach to ensuring high-quality and timely access to CKM care. The interdisciplinary CKM team would be supported by a CKM coordinator and would include representation from primary care, cardiology, nephrology, endocrinology, pharmacy and nursing, as well as care navigators, social workers, or community health workers. CKM coordinators or other health care professionals would assist with organizing the CKM team and facilitating communication with health care professionals.

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Table 5. Interdisciplinary Care Models in CKM Syndrome

Value-based care	Volume-based care
Involvement of interdisciplinary care team when any 2 of the following are present: CKD, diabetes, and subclinical/clinical CVD Use of a CKM coordinator, supporting an interdisciplinary team that includes representation from primary care and subspecialties (nephrology, endocrinology, cardiology), as well as pharmacy, nursing, and community health/care navigator Interdisciplinary team to develop clinical protocols based on CKM health guidance and related guidelines Cases of greater complexity/not easily addressed by protocols to be discussed at regular meetings of interdisciplinary team Recommendations conveyed to primary provider by CKM coordinator by EHR for discussion	Targeted referrals of high-risk patients to subspecialists. Potential thresholds: Nephrology for higher KDIGO risk: G3a (A3, especially if unresponsive to ACE inhibitor/ARB, G3b (A2/A3), G4, and G5 Endocrinology for diabetes with poor glycemic control (HbA1c >9%) or microvascular disease and/or end-organ damage Cardiology for prevalent CVD; can consider for high-risk subclinical CVD (eg, markedly elevated CAC score* or combination of elevated cardiac biomarker and echocardiography abnormality) CKM coordinator assistance with patient navigation across multiple subspecialists In health centers/regions with lower density of subspecialists, flexibility to rely more on telemedicine or CKM coordinator/interdisciplinary team and value-based care approach

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CAC, coronary artery calcium; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; EHR, electronic health record; HbA1c, hemoglobin A1c; and KDIGO, Kidney Disease Improving Global Outcomes.

*CAC score ≥300 in nonolder adults (men <65 y of age or women <75 y of age) and/or those with multiple CKM risk factors or CAC score ≥1000.

According to the severity and associated risk of the clinical condition or the complexity of the care plan, targeted additional referrals to subspecialists to activate volume-based additional expertise will ensure that higher-risk patients with CKM syndrome are identified and their care is further optimized. Suggested criteria for such targeted referrals are provided in Table 5. For patients seeing multiple subspecialists, CKM coordinators can additionally assist with patient navigation across multiple members of the health care team to support harmonized care.

Addressing SDOH

To address social determinants that affect CKM health, systematic screening for SDOH should be integrated into clinical care to identify patients with social needs and link them to available resources. Existing tools should be used to screen for key social needs, including financial strain (ie, food and housing insecurity, transportation and health care access), education/literacy, personal safety and mental health. There should be high-level awareness and policy support across health systems to address implementation challenges, especially when geography and structural racism impede access to healthy nutrition, neighborhood safety and walkability and individual-level access to community-based care.[92,93] Health care systems should consider screening tools that also assess health behaviors affected by social determinants (ie, physical activity and tobacco/alcohol use). The Oregon Community Health Information Network[77] and Centers for Medicare & Medicaid Services[74] screening tools that assess both key social needs and health behaviors are good examples of such instruments. Existing community resources and programs should be systematically identified, validated and leveraged to address social needs. Last, an existing screening tool like the Oregon Community Health Information Network or Centers for Medicare & Medicaid tool should be incorporated into the clinical care workflow and electronic health records for efficient implementation of care models addressing social determinants. Within an integrated care team, social workers, case managers, community health workers, or patient navigators can screen and connect patients to available social needs resources to support more equitable CKM care.

Stage-Specific Considerations

Stage 0 CKM: No CKM Risk Factors

The goal in caring for patients with stage 0 CKM is to maintain normal anthropometric values, normoglycemia, normotension and normal lipid profiles to minimize risk for the development of CKD or CVD. The AHA's Life's Essential 8 construct provides a holistic framework for the achievement, maintenance and surveillance of cardiovascular health in the population. Among cardiovascular health metrics, the prevention of obesity is a principal focus in primordial CKM syndrome prevention because of its causal role in type 2 diabetes, hypertension and hypertriglyceridemia.

The promotion of a healthy diet and regular physical activity is fundamental to the prevention of excessive weight gain in childhood,[94] with school-based lifestyle programs showing particular promise and reach.[95] In primary care settings, data support routine weight monitoring and counseling for healthy diet and regular physical activity with an emphasis on family involvement. To support healthy lifestyle and prevent the development of CKM risk factors with aging, there is need to optimize maternal CKM health (even before a woman becomes pregnant) to reduce the likelihood of future CKM syndrome in offspring; to ensure proper health education; to implement lifestyle interventions and deploy resources to thwart the development of CKM risk factors in younger populations, especially the avoidance of weight gain with associated increased metabolic risk; and to target the social environments in which individuals live, eat, play, and work by addressing SDOH.[96,97]

Stage 1 CKM: Excess or Dysfunctional Adiposity

The goal of management in stage 1 CKM is to address the presence of excess or dysfunctional adiposity

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to prevent metabolic risk factor development. BMI and waist circumference should be measured in concert, with the presence of abdominal obesity (waist circumference ≥88 cm in women and ≥102 cm in men, with lower cut points of 80 and 90 cm for those from Asian populations[98]) indicating a priority group for weight loss efforts. Reflecting central adiposity, waist circumference provides particularly powerful prognostic information on metabolic risk and the need for weight loss in those with grade I obesity and overweight. In addition, individuals with impaired glucose tolerance or prediabetes, regardless of BMI, should be prioritized for lifestyle modification and weight loss efforts.

Weight loss discussions should follow a patient-centered framework such as that provided by the Strategies to Overcome and Prevent Obesity Alliance.[99,100] For those individuals with obesity or impaired glucose tolerance, support for lifestyle modification is indicated, with an integrated multidisciplinary team available as needed to support weight loss efforts. At least 5% weight loss should be targeted, with greater benefits with greater weight loss. Pharmacotherapies and bariatric surgery are adjunctive options for those with BMI ≥30 and 40 kg/m^2, respectively, who are unable to achieve weight loss goals with lifestyle modification. For individuals with persistent/progressive glucose intolerance despite lifestyle modification, metformin can be considered to prevent progression to diabetes.

Stage 2 CKM: Metabolic Risk Factors and Kidney Disease

The goal of management in stage 2 CKM is to collectively address metabolic risk factors and CKD, with the primary goal of preventing progression to subclinical and clinical CVD.

MetS, Hypertriglyceridemia, and Hypertension

The presence of MetS indicates systemic metabolic dysregulation linked to abdominal/ectopic fat and insulin resistance and should trigger intensified lifestyle modification to address both the diagnostic and unmeasured (inflammation, hypercoagulability, endothelial dysfunction) components of MetS. Most individuals with type 2 diabetes have concomitant MetS, which contributes significantly to CVD risk in that population.[101] Optimal cardiovascular risk reduction for MetS involves lifestyle change followed by targeted pharmacotherapy for residually uncontrolled blood pressure, glycemia and lipids. In individuals at intermediate risk for ASCVD, MetS is a risk enhancer that favors statin use for ASCVD risk reduction.[67a]

Hypertriglyceridemia increases ASCVD risk and is frequently related to MetS and insulin resistance. Thus, after secondary causes are ruled out, lifestyle modification is first-line therapy. Statin therapy is advised for residual hypertriglyceridemia in those with intermediate or higher estimated ASCVD risk to lower ASCVD risk and modestly reduce triglycerides (10%–30%). For individuals with triglycerides ≥500 mg/dL, who are at increased risk for pancreatitis, use of fibrate therapy is advised, with fenofibrate preferred with concomitant statin therapy for fewer side effects. For individuals with triglycerides of 135 to 499 mg/dL in the setting of diabetes and additional risk factors, icosapent ethyl may be considered to lower ASCVD risk.

Hypertension management should follow established guidelines, with lifestyle modification, adoption of a balanced low-sodium diet, and use of pharmacotherapy as needed.[102] A blood pressure of <130/80 mm Hg is the goal in those with and without diabetes. Use of an RAAS inhibitor should be part of the antihypertension regimen for patients with diabetes with albuminuria and patients with CKD for additional protection of kidney function.

Diabetes

The approaches for CVD prevention in type 2 diabetes include lifestyle modification; achieving targets for control of HbA1c, blood pressure and cholesterol; and using medications that lower the risk of CVD, including antihyperglycemic, lipid-lowering and antiplatelet medications.[68] Lifestyle modification includes achieving and maintaining a healthy weight with behavior modification, healthy diet, recommended physical activity level and pharmacological/surgical approaches as needed. Stress management, healthy sleep and not smoking are additional components of a holistic approach to cardiovascular health. Appropriate targets for HbA1c and blood pressure include an HbA1c <7% for nonpregnant adults without significant hypoglycemia and blood pressure goal <130/80 mm Hg. Because most individuals with diabetes have at least intermediate ASCVD risk, moderate- to high-intensity statin therapy is advised, with consideration for adding ezetimibe to statins for those with high predicted ASCVD risk with the goal of lowering LDL cholesterol by ≥50%. Use of an SGLT2 inhibitor or GLP-1RA is advised for CVD risk reduction in those with high predicted CVD risk or selected comorbidities. SGLT2 inhibitors can be prioritized for those with CKD given their protective impact on kidney function decline, HF hospitalizations and major adverse cardiovascular events.[103] GLP-1RAs can be prioritized for those with grade II or higher obesity (BMI ≥35 kg/m^2), HbA1c ≥9%, or high insulin dose given their impact on weight, insulin resistance and reduction in major adverse cardiovascular events. Metformin use with SGLT2 inhibitor or GLP-1RA is advised for those with HbA1c ≥7.5% to help achieve glycemic targets with minimal side effects and better affordability.

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Chronic Kidney Disease

Addressing comorbid traditional CVD risk factors remains key in patients with CKD. For hypertension, especially in the setting of proteinuria, which is an independent CVD risk factor (particularly for HF), ACE inhibitors/ARBs are the first-line treatment. The use of SGLT2 inhibitors should be extended to all patients with CKD (at moderate or higher risk per the KDIGO classification), regardless of diabetes status, to protect kidney function and to reduce rates of HF hospitalization and cardiovascular mortality.[103] SGLT2 inhibitors can be safely initiated for patients with eGFR ≥20 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$. In patients with diabetic kidney disease and proteinuria on ACE inhibitors/ARBs, finerenone may be considered to reduce adverse cardiovascular and kidney events.[104] Finerenone can likely be initiated on background SGLT2 inhibitor therapy for those with eGFR >25 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ and potassium <5 mEq/L, although definitive data on concurrent use of these agents are pending. For hyperlipidemia management, CKD is a risk enhancer favoring statin therapy in intermediate-risk patients. Statin therapy and ezetimibe can be considered to lower risk of a first major atherosclerotic event in patients with CKD, especially in patients not on dialysis.[105,106]

Stage 3 CKM: Subclinical CVD and Risk Equivalents in CKM

The goal of management in stage 3 CKM is to intensify preventive interventions in those with subclinical CVD, very high-risk CKD, or high predicted CVD risk to prevent progression to clinical CVD and kidney failure.

Subclinical ASCVD

The presence of subclinical atherosclerosis as evidenced by CAC is associated with an increased risk in the general population[52] and among those with various CKM risk factors, including CKD[107,108] and diabetes.[109] A higher burden of subclinical atherosclerosis should prompt initiation of statin therapy, especially high-intensity statin therapy, as a result of a high baseline risk for ASCVD events. Beyond statin therapy, the presence and high burden of CAC (both absolute score ≥100 and elevated percentiles to identify young patients with high relative atherosclerosis burden) may support identification of candidates for additional therapies to support ASCVD risk reduction, including aspirin therapy, PCSK9 inhibitor, icosapent ethyl for hypertriglyceridemia, antihypertensive therapy and GLP-1RAs in various subgroups of patients with CKM.[110] Although the absence of CAC is generally associated with a lower risk of future ASCVD events, the "warranty period" of a zero CAC score (the expected time interval for conversion from CAC=0 to CAC >0) may be shorter in individuals with CKM syndrome given their high risk factor burden and a high lifetime risk despite relatively low short- to intermediate-term risk.[111–113] The 2018 AHA/American College of Cardiology cholesterol guidelines recommend strong consideration of statin therapy for all patients with diabetes who are 40 to 75 years of age even in the presence of a zero CAC score.[67b]

Subclinical HF

As per current HF guidelines, subclinical HF is defined as the presence of abnormal cardiac structure or function on cardiac imaging or elevated cardiac biomarkers (NT-proBNP, high-sensitivity cardiac troponin, or both). Subclinical HF, particularly the combination of both echocardiographic and cardiac biomarker abnormalities, is associated with an increased absolute risk of progression to clinical HF.[54] In addition to treatment of cardiovascular risk factors and underlying comorbid conditions, for those with asymptomatic left ventricular systolic dysfunction, treatment with ACE inhibitors/ARBs and β-blockers is advised to decrease progression to symptomatic HF and to potentially reduce mortality. The use of an SGLT2 inhibitor in patients with type 2 diabetes reduces the likelihood of incident HF hospitalizations and cardiovascular mortality.[115] These agents should be prioritized in patients with type 2 diabetes and stage B HF given their high absolute HF risk. Biomarker-guided strategies for disease prevention have been studied[116] and may prevent overt HF in high-risk individuals, although further studies are needed to establish clinical benefit, cost-effectiveness and optimal screening strategies for such an approach.

Risk Equivalents in Stage 3 CKM

Individuals with very high-risk CKD per the KDIGO heat map or those with high predicted CVD risk are also included in stage 3 CKM. The threshold for high risk will be further elucidated by applying the new CKM risk prediction algorithm[88] to clinical trial data for assessments of net clinical benefit at different levels of predicted risk. Because of their high absolute CVD risk, this subgroup should also be prioritized for intensified preventive therapies, if contraindications are not present, with specific therapies based on CKM risk profiles. In addition, those with type 2 diabetes at high predicted risk or with multiple uncontrolled CKM risk factors may be a subgroup in whom the use of combined SGLT2 inhibitor and GLP-1RA therapy could be considered for greater absolute risk reduction for incident CVD events.

Stage 4 CKM: CVD in CKM With and Without Kidney Failure

The goal of management in stage 4 CKM is to optimize care and secondary prevention for patients with CVD and concurrent metabolic factors, CKD, or both. In all patients with ASCVD, use of aspirin or $P2Y_{12}$ inhibitors in addition to high-intensity statin therapy is indicated,

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with consideration for additional LDL cholesterol–lowering agents such as ezetimibe and PCSK9 inhibitor based on the presence of high-risk ASCVD and LDL cholesterol thresholds as per current guidelines. Nonstatin LDL cholesterol–lowering agents such as PCSK9 inhibitor, bempedoic acid and inclisiran should be considered for those with statin intolerance. Guideline-directed medical therapy (GDMT) is also indicated for all patients with HF as per current guidelines, with a particular focus on the 4 pillars of β-blockers, angiotensin receptor/neprilysin inhibitors, mineralocorticoid receptor antagonists and SGLT2 inhibitors for patients with HFrEF. In stage 4 CKM, different CKM risk factors indicate the need for additional therapeutic considerations.

Obesity, MetS and CVD

Among individuals in stage 4 CKM, BMI and waist circumference should be measured at least annually among individuals with existing CVD, with the presence of obesity and abdominal obesity indicating particular need for weight loss. Weight loss discussions should follow an approach such as that outlined by the Strategies to Overcome and Prevent Obesity Alliance toolkit.[99]

Intentional weight loss should be a therapeutic goal among individuals with obesity and prevalent CVD. Moderate intentional weight loss (5%–10%) should be targeted to improve metabolic risk factor control among patients with CVD and to improve functional status and quality of life in patients with HF.[117] Marked intentional weight loss (>10%) should be targeted to potentially improve cardiovascular outcomes in individuals with prevalent CVD.[118,119]

The initial focus should be lifestyle modification, with behavior change, moderate caloric restriction and regular physical activity. Weight loss should be supported by an integrated multidisciplinary team to facilitate lifestyle modification, with the adjunctive approaches of obesity pharmacotherapy (for BMI ≥27 kg/m^2) and metabolic surgery (for BMI ≥35 kg/m^2) available to further reduce weight and cardiometabolic risk. Among pharmacotherapies, use of incretin analogs (GLP-1RAs, GLP-1/GIP (glucose-dependent insulinotropic polypeptide)-RAs, GLP-1/GIP/glucagon-RAs) should be prioritized because they induce marked intentional weight loss and improve metabolic risk factor control. Furthermore, initial reports from the forthcoming SELECT clinical trial (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity) indicate that high-dose GLP-1RAs reduce cardiovascular events in patients with obesity and CVD. Pending full trial results, this finding may support the use of these agents as front-line therapy in patients with obesity and established CVD.

The presence of MetS and hypertriglyceridemia should trigger further intensification of lifestyle modification. Marked hypertriglyceridemia (≥500 mg/dL) is an indication for fibrate therapy (fenofibrate in concert with statin therapy), and for modest hypertriglyceridemia (135–499 mg/dL), the use of icosapent ethyl should be considered. In hypertension, the goal for blood pressure management is <130/80 mmHg with lifestyle and pharmacotherapy. In individuals with CKD or diabetes, special pharmacological considerations include ACE inhibitors/ARBs and a steroidal mineralocorticoid receptor antagonist for those with resistant hypertension. For Black individuals with HFrEF, hydralazine/isosorbide should be prioritized after the 4 pillars of GDMT in those with persistent uncontrolled hypertension.

Diabetes and CVD

In patients with diabetes and CVD, lifestyle modification, multicomponent risk factor control with pharmacological agents as needed, and intensified use of cardioprotective lipid-lowering and antihyperglycemic therapies are fundamental to the therapeutic approach. Many individuals with diabetes and ASCVD will fall into the subpopulation with very high-risk ASCVD, for whom intensified LDL-lowering therapy with ezetimibe and a PCSK9 inhibitor or another agent could be considered for LDL ≥70 mg/dL on maximally tolerated statin therapy.[67a,120]

For patients with diabetes and ASCVD, an SGLT2 inhibitor or GLP-1RA is advised to reduce the risk for major adverse cardiovascular events and cardiovascular mortality, with the SGLT2 inhibitor additionally reducing risk for HF hospitalization.[68] A comorbidity-based approach is suggested for choosing between these agents for those with diabetes and ASCVD, with an SGLT2 inhibitor suggested for those with CKD or concomitant HF and a GLP-1RA advised for those with BMI ≥35 kg/m^2, with HbA1c ≥9%, or on high insulin doses.[68] The indications for dual use of SGLT2 inhibitor and GLP-1RA are not yet well defined but could be considered for those with high-risk ASCVD or with ASCVD and combinations of the aforementioned comorbidities.

An SGLT2 inhibitor is indicated for all patients with HF regardless of diabetes status to reduce HF hospitalizations and cardiovascular mortality and to improve quality of life.[90] As per current guidelines, dipeptidyl peptidase 4 inhibitor and thiazolidinediones are contraindicated in patients with HF and should largely be avoided. The addition of GLP-1RA to an SGLT2 inhibitor in patients with diabetes and HF can be considered for those with BMI ≥35 kg/m^2, with HbA1c ≥9%, on high insulin doses, or at increased risk for adverse outcomes due to coexisting ASCVD and HF or multiple severe comorbidities.

The use of metformin in concert with cardioprotective antihyperglycemic therapies, particularly SGLT2 inhibitors, helps to achieve glycemic targets with minimal side effects and is advised for those with HbA1c >7.5% or on insulin, with eGFR ≥30 mL·min^{-1}·1.73 m^{-2}, and without unstable or decompensated HF.

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CKD and ASCVD

In patients with concomitant ASCVD and CKD, moderate- to high-intensity statins are recommended as part of optimal medical therapy for ASCVD and CKD.[41] Medications that preserve kidney function and reduce cardiovascular death such as SGTL2 inhibitors should be prioritized, regardless of diabetes status.[121] For those who have not achieved individualized glycemic targets despite metformin and SGLT2 inhibitor or who are unable to use those medications, a long-acting GLP-1RA is recommended.[103] Finerenone can be considered to reduce adverse cardiovascular and kidney events in patients with diabetes and CKD already on maximally tolerated renin-angiotensin system inhibition,[104] with or without SGLT2 inhibitor use.

CKD and HF

The systematic underuse of high-quality evidence-based therapies for CVD in patients with kidney disease, historically referred to as renalism,[122] remains a significant barrier to GDMT optimization in HF with CKD. This paradigm extends to representation of patients with CKD in CVD trials, with a sharp decrease in trial enrollment below an eGFR <30 mL·min^{-1}·1.73 m^{-2}, and even less so with kidney failure/kidney transplantation. Paradoxically, patients with stage 4 and 5 CKD with kidney failure have the highest rates of adverse cardiovascular outcomes, including premature mortality. Reflecting the above conundrum, major HF guidelines have less granular guidance on GDMT (especially RAAS inhibitors) in HF with stage 4 and 5 CKD, dialysis and transplantation.

SGLT2 inhibitors are recommended for all patients with CKD and HF, regardless of ejection fraction, diabetes status, and baseline UACR.[123,124] These agents can be initiated up to an eGFR of 20 mL·min^{-1}·1.73 m^{-2} and maintained until the point of kidney replacement therapies. Ongoing trials will shed light on the scope of the use of SGLT2 inhibitors in patients on maintenance dialysis or recipients of kidney transplant allografts (NCT05374291). An angiotensin receptor/neprilysin inhibitor in HFrEF is preferred over ACE inhibitors/ARBs,[125,126] with consideration for a reduced dose of sacubitril-valsartan (24/26 mg twice daily) with eGFR <30 mL·min^{-1}·1.73 m^{-2}.[127] Angiotensin receptor/neprilysin inhibitor use is also associated with a slower decline in kidney function and lower adverse kidney events[126,128] with incremental value in blood pressure control across the eGFR spectrum.[129] ACE inhibitors/ARBs can be maintained in patients with eGFR <30 mL·min^{-1}·1.73 m^{-2} and HFrEF with frequent monitoring for hyperkalemia. Dose titration can be achieved in accordance with the KDIGO guidance for renin-angiotensin system inhibitor use in CKD with careful monitoring for uremic symptoms and factoring in timing and need for kidney replacement therapy.[41]

Use of components of GDMT such as angiotensin receptor/neprilysin inhibitors/ACE inhibitors/ARBs and mineralocorticoid receptor antagonists may be limited by the presence of CKD, including concerns for worsening renal function and hyperkalemia.[130] The use of potassium binders and simultaneous use of agents such as SGLT2 inhibitors or angiotensin receptor/neprilysin inhibitors may be associated with lower rates of hyperkalemia and hence may be considered to assist in optimization of GDMT use.[126,130] Fluctuations in serum creatinine with decongestion and GDMT use are driven largely by expected and intended changes in glomerular hemodynamics and should not prompt immediate discontinuation of these medications.[131]

Atrial Fibrillation Management in Stage 4 CKM

Several CKM factors are linked to a greater likelihood and burden of atrial fibrillation, including hypertension, obesity, CKD and dyslipidemia.[57] Therefore, major guidelines recommend comprehensive risk factor control in patients with atrial fibrillation.[120] In addition, the CKM factors of diabetes and hypertension increase stroke risk in atrial fibrillation, favoring the use of anticoagulation for stroke prophylaxis. When anticoagulation is indicated, recent guidelines support the use of either dual oral anticoagulants or warfarin in patients with CKM, including those with severe obesity or CKD, although dose adjustments for direct oral anticoagulants are needed in patients with advanced kidney disease. Weight loss, regular physical activity and improved cardiorespiratory fitness are advised to decrease atrial fibrillation burden and severity in patients with CKM.[57] Treatment of obstructive sleep apnea, which is closely linked to obesity, may also help to reduce atrial fibrillation burden.

Stage 4b CKM: Kidney Failure

The risk of CVD is disproportionately elevated in patients with kidney failure on maintenance dialysis, with HF and ASCVD representing the 2 major phenotypes in this population.[132] Although there are limited high-quality data to guide best practices for HF and ASCVD management in kidney failure, certain therapies have shown benefit, especially with HF-related outcomes, in this population. Strong consideration should be given to frequent dialysis sessions to reduce left ventricular hypertrophy/left ventricular mass index and HF hospitalizations and to improve quality of life.[133–135] When medication classes such as β-adrenergic receptor blockers or ACE inhibitors are used, the dialyzability of these agents and their timing with the dialysis cycle should be factored into the treatment plan.[136] Ongoing trials are looking at potential cardiovascular benefits with the use of steroidal mineralocorticoid receptor antagonists (NCT01848639, NCT03020303) and SGLT2 inhibitors (NCT05685394, NCT05179668, NCT05374291) in patients on dialysis. There is a limited role for routine initiation of statins in patients on dialysis without known ASCVD, but continuation of these agents

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when initiated before dialysis initiation is reasonable.[137] Last, given the high burden of pulmonary hypertension and right ventricular failure unique to the milieu of kidney failure and the process of kidney replacement therapy, an early multidisciplinary approach with advanced HF specialty involvement is recommended as part of the comprehensive CKM care approach for these patients.[138]

Confluence of CKM Factors

In patients with combined CVD, metabolic risk factors, and CKD, selecting the most appropriate GDMT therapy requires consideration of the phenotype of CVD disease, the presence of coexisting conditions, and the expected net benefit of therapies, especially with advanced CKD. The interplay of comorbid conditions, especially CKD, adds complexity to the management of HF and requires careful monitoring for hyperkalemia when GDMT is implemented.[121,139] In patients with a propensity for hyperkalemia, the addition of an oral antihyperkalemic agent such as patiromer acetate or sodium zirconium cyclosilicate may allow maintenance of an RAAS inhibitor without the risk of hyperkalemia.[140] For patients with CKD and diabetes, especially in the setting of HF, additional antihyperglycemic agents beyond SGLT2 inhibitors may be necessary to achieve glycemic control because the glucose-lowering effects of SGLT2 inhibitors are modest. For patients with diabetes who are unable to use metformin with an SGLT2 inhibitor for enhanced glycemic control due to eGFR <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ or decompensated HF, GLP-1 agonists are effective for lowering glucose, are not appreciably affected by worsening kidney function, and are generally considered safe in patients with advanced CKD.[141]

CKM Stage Regression

The CKM staging paradigm also presents an opportunity to promote CKM stage regression, by which favorable changes in CKM pathology over time result in the "loss" of criteria for a given CKM stage. This is achieved most reliably through marked intentional weight loss and significant lifestyle changes, which have been associated with reductions in adipose tissue and improvements in glucose tolerance (stage 1)[142,143]; remission of diabetes,[142] hypertension,[144] hyperlipidemia,[143] and MetS, as well as improvements in kidney function[145] (stage 2); and reversals of adverse cardiac remodeling[146] (stage 3). Therefore, it is advised that opportunities to improve CKM health for those in more advanced CKM stages are emphasized in clinical encounters and educational campaigns.

CALL TO ACTION

Optimizing CKM health in the population will require a multifaceted, concerted and patient-centered effort involving multilevel partnerships among clinical entities, policymakers, payers, and numerous stakeholders, as well as the enhancement of education and research related to CKM syndrome. It will also necessitate changes to clinical workflows, care team composition, insurance coverage and reimbursement strategies to support interdisciplinary care, integrated obesity management, consideration of SDOH and equitable access to pharmacotherapies, and application of proven strategies to support implementation of CKM guidance within and across health centers (Figure 5).

Consideration of SDOH

SDOH play a critical role in CKM health, and health care systems must implement prevention and treatment models that reflect an SDOH focus.[69] Specifically, social needs screening tools must be used across electronic health record platforms to reach diverse patient populations.[147] In addition, health care systems can address social needs among patients with CKM syndrome by identifying, using and referring to existing community resources. Within health care systems, interdisciplinary care teams should include care navigators, social workers, or community health workers who can connect patients to community-based resources that protect against the effects of adverse social conditions. Ultimately, we need to collect data on the impact of addressing SDOH and providing more equitable access to resources for a healthy lifestyle on CKM-related health behaviors and outcomes. For example, as the AHA's Food Is Medicine Initiative[148] begins, future work should investigate how this initiative changes CKM syndrome prevalence to inform strategies to promote nutrition access and to improve CKM-related outcomes.

Interdisciplinary Care

There is an urgent need to minimize the chasm between the availability of foundational therapies that improve the life span and health span of individuals with CKM syndrome and their implementation at a population level. Several barriers limit effective implementation of these agents, including a fragmented health care delivery system, specialty silos, disparities in access to specialty care and therapies, financial toxicity of the newer pharmacotherapies, and clinician inertia.[149] There is a need for disruptive models of CKM health care delivery to improve clinical outcomes with effective use of available knowledge and therapies. The value- and volume-based approaches provided in this advisory represent complementary approaches for facilitating harmonization of clinical management across specialties and enhancing holistic CKM care. The use of CKM coordinators can enhance collaboration with and support for primary care physicians and assist with

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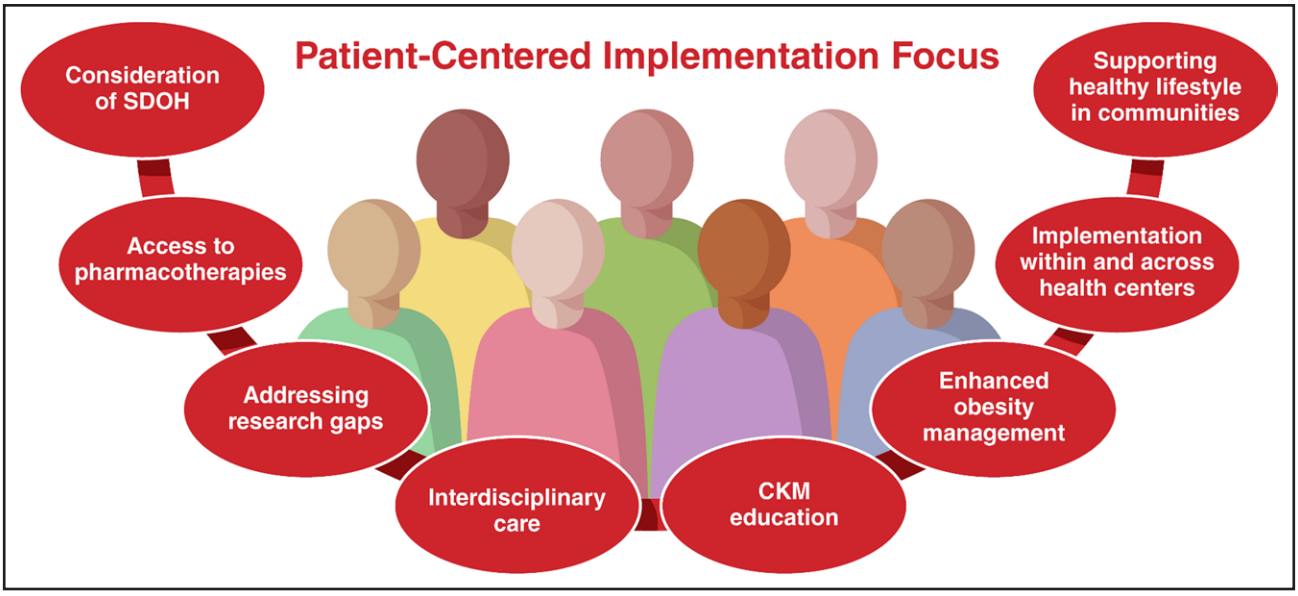

Figure 5. Components of a CKM syndrome call to action.
The components of the call to action for optimizing cardiovascular-kidney-metabolic (CKM) health in the population include (1) systematically considering social determinants of health (SDOH) in the care model for CKM syndrome; (2) enhancing access to pharmacotherapies that positively affect outcomes related to CKM syndrome; (3) addressing research gaps related to CKM syndrome; (4) facilitating interdisciplinary care and reducing care fragmentation; (5) improving the education of health care professionals and the lay community related to CKM syndrome; (6) enhancing management of obesity as the root cause of much of CKM syndrome; (7) implementing CKM syndrome care models within and across health centers; and (8) building multistakeholder partnerships to support healthy lifestyle and the achievement of ideal cardiovascular health across diverse communities.

patient navigation across multiple specialists. In health centers/regions with a lower density of subspecialists, the flexibility to rely more on telemedicine or on the CKM coordinator and interdisciplinary team will help overcome existing variability in access to subspecialists and prolonged wait times.[150] Such an interdisciplinary care model would represent a shift in the framework of existing reimbursement metrics and criteria and would need to be supported at a systems level with necessary health care policies and the buy-in of all involved stakeholders.

Access to Pharmacotherapies

Overwhelming evidence demonstrates the benefit of antihyperglycemic medications such as SGLT2 inhibitors and GLP-1RAs to manage and prevent adverse CVD events and CKD progression. Unfortunately, these medications remain underprescribed and underused because of clinician prescribing patterns and lack of affordability and access, attributable to prohibitive out-of-pocket costs and formulary restrictions.[151,152] Although balance is critical in the implementation of effective yet currently expensive medications, a restrictive and myopic approach to therapies with proven cardiovascular and kidney benefits could result in missed downstream opportunities to improve CKM health and to reduce global health care costs.[153] Health care professionals, health care systems, insurance companies, industry, patients and payers need to align goals and incentives through advocacy and policy to increase the use of these effective therapies.

Research Gaps

CKM syndrome is common, deadly and treatable, yet numerous knowledge gaps drive the need for focused research in key areas. For the development of CKM syndrome, incomplete understanding exists of sex differences; genetic underpinnings and applications of genetic testing; mechanisms of vascular, myocardial and kidney dysfunction; and environmental and community-level risk factors. The mechanisms linking CKM risk factors to CVDs and CKD, both individually and combined, also remain unclear. Molecular determinants and pathways of progression from subclinical to overt disease are largely unknown. Identification of intermediate pathways intersecting CKD and CVD such as inflammation and feed-forward loops could provide new targets for interventions. Assessment of risk severity for CKM syndrome is required to inform interventions, as well as their sequence and timing. Beneficial interventions for various CKM syndrome stages and risks must be identified. Clearer understanding of CKM risk–based implementation of protective therapies such as SGLT2 inhibitors, GLP-1RAs, and RAAS inhibitors and the interactions between CVD and CKD treatments is necessary. Strategies for applying combination therapies, along with

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evidence-based approaches for initiating, monitoring (such as frequency of UACR on therapy and targets for UACR reduction), and sustaining them, are essential and represent areas for future research.

CKM Education

Given the significant burden of CKM syndrome both in the United States and globally, a key component of the CKM health call to action is commitment to improving comprehensive awareness and education. An evidence-based curriculum should guide health care professionals on the identification of CKM risk and facilitate clinician-supportive tools to enhance risk prediction across the spectrum of CKM stages, in addition to sharpening a focus on prevention and management. Education should be a priority for people living with CKM risk, as well as underresourced families and communities. An integrated people-centered approach should involve all stakeholders, including multidisciplinary care teams, health systems, public health professionals and influencers of policy. The implementation of guidelines will be enhanced by simplification and harmonization. Although education is essential to improving CKM health, applying knowledge to clinical practice and facilitating the alignment of incentives with best practices are vital.

Enhanced Obesity Management

Despite decades of advancement in our scientific understanding of the pathophysiology underlying obesity and its CKM consequences, a substantial gap remains between that knowledge and the successful implementation of obesity management in clinical practice. Because obesity is a major driver of CKM syndrome, enhanced prevention and management of obesity is a clinical and public health priority. It is critical that health care professionals across subspecialties receive training in obesity medicine. The use of established toolkits for addressing obesity will support health care professionals in effectively initiating obesity discussions. It is also crucial that patients achieve access to and support for enhanced obesity management options such as lifestyle/behavioral therapies, pharmacotherapies and bariatric surgery. Integrated multidisciplinary teams support effective, patient-centered approaches for weight management and should be prioritized for those with CVD and high CKM risk. A framework for the delivery of enhanced obesity care is needed in early CKM stages, with health policy interventions that are flexible and adaptable to diverse patient groups. Building enhanced obesity management requires substantial financial input and engagement from multiple stakeholders but is likely to result in lower morbidity and mortality, long-term health care cost savings, and improved quality of life for patients with and at risk for CKM syndrome.

Implementation Within and Across Health Centers

The AHA's Get With The Guidelines registry network provides a ready framework of health care systems for the rapid implementation of key CKM health measures, especially in limited-resource communities and underresourced hospital systems. Data on cardiovascular and kidney adverse outcomes, biomarkers and SDOH will significantly contribute to the collective knowledge on optimizing care for patients with CKM syndrome across a broad network of health care systems. An assumption of publicly reporting performance on process of care measures is that care and outcomes will be better at those hospitals doing well on those metrics. Informed by the AHA's CKM health initiative, validated CKM health measures and center-specific performance across registry-based data will provide the opportunity to leverage and scale a well-developed national learning health system implementation science framework. This will translate into a viable and patient-centric AHA CKM health certification program across Get With The Guidelines hospitals in the United States and globally, allowing the designation of AHA Centers for CKM Health Excellence for institutions that meet the criteria for optimal implementation of prespecified CKM health metrics.

Supporting Healthy Lifestyle in Communities

Because of the close link between SDOH and CKM, there is a higher burden of CKM syndrome in more disenfranchised communities. Although achieving ideal cardiovascular health lowers CKM risk, SDOH at multiple levels impair the ability of many to engage in a healthy lifestyle and self-care. The strategies to interrupt disparities in CKM begin with identifying the populations at risk and are addressed by directing resources toward those individuals to promote cardiovascular health. Interventions built with community engagement can build trust to codesign intervention tools, including digital health technology, that can be leveraged to promote CKM health. Multilevel interventions targeting both the individual and social and structural factors such as access to health-promoting resources, including health care, food and safe housing, have the greatest impact at the population level. However, structural interventions that are implemented through policy are most effective when supported by educational strategies that educate the populations at greatest risk. Multilevel partnerships among various stakeholders, including governmental and public health agencies, health care organizations, insurance companies, employers and community-led advocacy organizations, are needed to incentivize healthy

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choices and to enhance cardiovascular health across the life course and across diverse communities.

CONCLUSIONS

CKM health reflects the intricate interrelationships among metabolic risk factors, CKD, and the cardiovascular system. Poor CKM health has significant implications for adverse clinical outcomes, most notably cardiovascular morbidity, and premature mortality. However, there is a growing array of therapies and health care strategies that have great potential to improve outcomes for the patient with CKM syndrome. The development of a clear definition and staging framework for CKM syndrome, the enhancement of CKM risk prediction algorithms, and the clarification of approaches to CVD prevention and management in patients with CKM syndrome provide a critical foundation for improving CKM health and related outcomes in the population.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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